A Dissertation on

A STUDY ON SERUM LEVELS OF C–REACTIVE PROTEIN AND ITS RELATION TO CLINICAL AND LABORATORY PROFILE OF ASYMPTOMATIC CASES DIAGNOSED WITH FATTY LIVER DISEASE BY RADIOLOGICAL SCREENING.

Dissertation Submitted to

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

Chennai

In partial fulfillment of the regulations for the award of the degree of

M.D. BRANCH – I
GENERAL MEDICINE
APRIL 2012

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL
CHENNAI – 600 001

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA.

CERTIFICATE

This is to certify that the dissertation titled "**A study on serum levels of C–Reactive protein and its relation to clinical and laboratory profile of asymptomatic cases diagnosed with fatty liver disease by radiological screening**" is the bona fide original work of Dr. Deepu Sebin, in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamil Nadu DR. M.G.R Medical University to be held in APRIL 2012. The Period of study was from December 2010 – November 2011. I forward this to the Tamil Nadu Dr. M. G. R. Medical University, Chennai, Tamil Nadu, India

PROF. DR.S. MAGESH KUMAR, M.D.
Professor and Head

PROF.DR. K.S. CHENTHIL M.D.
Professor of Medicine

Department of Medicine
Govt. Stanley Medical College and Hospital
Chennai 600 001

Prof. Dr. S GEETHA LAKSHMI M.D., Ph.D.
D E A N
Government Stanley Medical College and Hospital
Chennai – 600 001

DECLARATION

I, **Dr. DEEPU SEBIN**, solemnly declare that the dissertation titled, "**A study on serum levels of C – Reactive protein and its relation to clinical and laboratory profile of asymptomatic cases diagnosed with fatty liver disease by radiological screening",** was done by me at Government Stanley hospital during the period 2010-2011 under the guidance and supervision of my unit Chief **Prof. K.S. CHENTHIL, M.D**. Professor of Medicine, Government Stanley Medical College and Hospital, Chennai. The dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD Degree (Branch-1) in General Medicine.

Place: Chennai Dr. DEEPU SEBIN

Date:

ACKNOWLEDGEMENT

I thank **Prof. Dr. S GEETHA LAKSHMI M.D.,PhD,** Dean, Government Stanley Medical College and Hospital for permitting me to use all the resources at her disposal for my dissertation. I am grateful to **Prof. Dr. S MAGESH KUMAR M.D.,** Professor and Head of the Department of Medicine, Stanley Medical College and Hospital for permitting me to do the study. I thank **Prof. Dr. K.S. CHENTHIL M.D.,** Professor of Medicine and Chief Unit VI, Stanley Medical College and Hospital for approving this study and giving valuable suggestions in preparing this dissertation. I express my particular thanks to **Prof. Dr. SUNDAR MD** former Professor of Medicine, Stanley Medical College and Hospital for his guidance during the study period. I am extremely thankful to my assistant professors **Dr. S.GEETHA M.D.,** and **Dr. V. RAJAKUMAR MD.,** for their valuable help and encouragement. I express my gratitude to **Dr. JAYANTHI M.D., D.M.,** former HOD and Professor of Gastroenterology, Government Stanley Medical College, for her valuable guidance and support. Finally, I wish to thank all the patients included in this study and my colleagues for their cooperation and support.

CONTENTS

1.INTRODUCTION

The diagnosis of Fatty liver is often, an uninvited one. Many a times the diagnosis of Fatty liver is made when the patient is undergoing radiological investigations like USG or CT scan of the abdomen for an unrelated purpose. And clinicians are seeing more and more cases of radiologically diagnosed, incidentally detected fatty liver disease. Increasing use of radiological diagnostic modalities, health checkups and screening programs and more over the epidemic of obesity and metabolic syndrome contribute to this phenomenon.

Fatty liver is a clinico - histopathologic entity. In simple terms it refers to the accumulation of fat (triglyceride vacuoles) in hepatocytes. Fatty liver disease can range from steatosis to steatohepatitis. This condition can occur with the use of alcohol (alcohol-related fatty liver) or in the absence of significant alcohol consumption (nonalcoholic fatty liver disease also known as NAFLD)

This study is an attempt to find more about such radiologically detected fatty liver disease in totally asymptomatic and otherwise healthy individuals. A diagnosis of Fatty liver is of no less significance, even when the patient is asymptomatic and appears totally healthy. It may be the first warning of a

potentially dangerous metabolic abnormality, toxic effect of alcohol abuse, drugs or some rare liver disorders. This finding warrants a detailed clinical and laboratory evaluation and targeted therapies.

Stanley Medical College caters to a large population of people in and around north Chennai. And the physicians here do come across a good number of radiologically diagnosed fatty liver disease. Moreover studies from the city have shown that there is a disproportionate prevalence of patients with metabolic abnormalities that results in high cardiovascular risk.

By this study a profile of such asymptomatic incidentally detected fatty liver patients is looked into. The proportion of alcohol and non alcohol related fatty liver disease is analysed. An effort is made to study the various clinical and biochemical abnormalities, its proportion, and association with metabolic syndrome. By this study a possible algorithm to approach such a case can be made out which is relevant to the study population (i.e., Northern Chennai). And in the next step high sensitive C reactive protein levels are being evaluated. Being a pro-inflammatory marker and an in depended cardiovascular risk factor, hsCRP may provide a clue regarding the cardiovascular risk status of such cases and also the potential link between all the metabolic abnormalities.

2.AIM OF THE STUDY

1. To assess the Clinical profile of asymptomatic cases diagnosed with Fatty liver by routine radiological screening methods like USG and CT Abdomen.
2. To study the laboratory pattern associated with alcoholic and non alcoholic causes of fatty liver disease.
3. To find out the proportion of alcoholic and non alcoholic fatty liver disease.
4. To obtain an idea about the prevalent and strongly associated metabolic anomaly associated with fatty liver disease.
5. To study the prevalence of Metabolic Syndrome in the group.
6. Assessment of serum levels of high sensitivity C - Reactive Protein, a marker of proinflammatory state and independent CAD risk factor in cases diagnosed with Fatty liver disease.
7. Evaluation of hsCRP levels with respect to the various clinical and biochemical abnormalities and find the correlation.

3.REVIEW OF LITERATURE

Fatty liver once a histopathological term used to denote fat accumulation in the liver now has become a clinical diagnosis based on imaging and biopsy. Microscopic examination a fatty liver is charactersied by inytracytoplasmic accumulation of triglycerides.[1] On ultrasound imaging the fatty liver produces a diffuse and non specific increase in echogenicity, which usually is compared with the kidneys.[2] Fatty liver disease is a common clinical condition which is fast assuming importance as a possible precursor of more serious liver disorders, including cirrhosis of the liver and hepatocellular carcinoma.

Classification

Fatty liver is classified mainly into Alcohol related and Non alcoholic Fatty liver disease.[3] The vast majority of cases in the Non alcoholic fatty liver group consist of patients with obesity, insulin resistance, hypertension and various lipid abnormalities.[4] And over the last few decades, the term Non alcoholic fatty liver disease became the representative term for such a disease profile. Nevertheless, non alcohol etiology can be many. Fatty liver, according to the recent literature is classified into the following. [5]

- Fatty Liver Disease related to alcohol etiology
- Non Alcoholic Fatty liver Disease (NAFLD)

    (1) Drugs and toxins

    (2) Metabolic abnormalities, either acquired or congenital

    (3) Surgical Procedures

    (4) Inborn Errors of Metabolism

Figure 3.1 Classification of Fatty liver

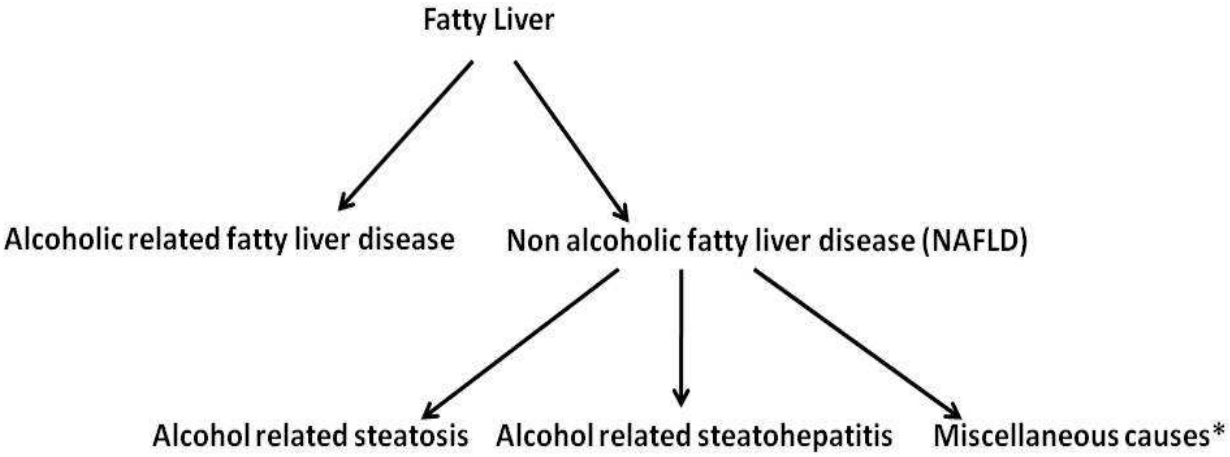


Table 3.1 Miscellaneous causes of fatty liver

Acquired Metabolic Disorders	Congenital Metabolic Disorders
Obesity Diabetes mellitus Hyperlipidemias Kwashiorkor and marasmus Starvation	Familial hepatosteatosis Galactosemia Glycogen storage disease Hereditary fructose intolerance Homocystinuria Systemic carnitine deficiency Tyrosinemia Weber-Christian syndrome Wilson disease Abetalipoprotenemia
Drugs and Toxins	**Surgical Conditions**
Cytotoxic Drugs Estrogen Chromates Barium salts Glucocorticoids Others Valproic acid	Extensive small bowel resection Gastric bypass Jejunoileal bypass Biliopancreatic diversion Severe Anemia TPN

The vast majority of fatty liver disease which present without alcohol etiology has a particular pattern. It is spectrum often compared with metabolic syndrome, a spectrum of obesity, insulin resistance, dyslipidemias and hypertension. The original intention and the literary meaning of NAFLD – Non alcoholic fatty liver disease was to include all causes of fatty liver other than alcohol. However since the most cases of non alcoholic fatty liver now represents the metabolic syndrome pattern, the term NAFLD has eventually became a representative of that group.

Non Alcoholic Fatty Liver Disease

Non alcoholic fatty liver disease is a common cause of chronic liver disease and its incidence is rising worldwide. Ever since Ludwing, Jurgen etal from Mayo clinic [7] described the histological finding in fatty liver and coined the term “Non alcoholic steatohepatitis (NASH)”, this terminology been studied, researched and published a lot, especially in the last decade. Non alcoholic fatty liver disease is now considered a spectrum of liver disease which can be benign (simple steatosis) or one which can inflict serious damage to liver and result in cirrhosis and

complications (steatohepatitis). Nonalcoholic fatty liver disease (NAFLD), encompasses simple fatty liver, NASH, and NAFLD-associated cirrhosis.

Defining Fatty Liver

Fatty liver can be defined by the presence of at least two of three abnormal findings on abdominal ultrasonography: diffusely increased echogenicity (‘bright') liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal. [8] NAFLD is highly likely provided that the other causes of liver disease have been rigorously excluded, particularly significant alcohol intake (more than 140 g weekly in men, 70 g weekly in women) and medication use. In patients with otherwise unexplained ALT elevation, NAFLD is highly likely to be the cause if hepatic imaging results are compatible with fatty liver, and metabolic risk factors are present. Serum ALT elevation secondary to other causes and preexisting liver diseases has to be ruled out.

NASH, a subset of NAFLD is the term used to describe the clinical entity in which patients lacking history of significant alcohol consumption but have liver biopsy finding similar to alcoholic steatohepatitis. [9]

Epidemiology

NAFLD was considered to be a disease prevalent in western and industrialized countries. However there is a considerable increase in prevalence rate detected from developed countries. [10,11,12] Studies report a prevalence of 20 to 40 percent in western population and 5 to 30 percent in Asia Pacific Population. [11, 13, 14]

Although in the general population, the prevalence of NAFLD and NASH are approximately 20% and 3% respectively, in obese population, NAFLD may even go up to 75% of the subjects.

Indeed, in morbidly obese, steatosis (NAFLD) has been found in almost all subjects, with NASH being present in 25%-70% of these individuals. It has been estimated that approx 70-75% of type 2 diabetic subjects may have NAFLD. However, these studies were mainly done in western populations. South Asians in general and Asian Indians in particular, have very high rate of diabetes, insulin resistance and premature CAD. [17]

Given below is a table of comparison of NAFLD prevalence in Asia, compiled from different studies [10-17]

Table 3.2 : Prevalence of NAFLD among Adult Population of Asia-Pacific Countries.

Country	Individuals with NAFLD (%)
Japan	9-30
China	5-24
Korea	~18
India	5-28
Indonesia	~30
Malaysia	17
Singapore	5

NAFLD IN INDIA

Overall prevalence of NAFLD is around 10-20% based on the data on people undergoing master health check up, ultrasongography for non-liver related causes, healthy relatives of hospitalized patients, and railway employees and their families. The epidemiological studies that have been carried out in various parts of India to find out the prevalence of NAFLD of studies using histological criterion to diagnose NAFLD, shows varying results.

Table 3.3 -Aggregated region wise prevalence of NAFLD in India, from various studies. [10,14,18]

Region	n	Male : Female	Prevalence	Study
West	210	2:1	55.4 ± 9	Amarapukar et al. , 2000
East	63	2:1	42.7	Singh et al., 2004
West	730	1:1	39.08 ± 12.3	Amarapukar et al., 2007
West	225	3:1	30± 12	Uchil et al., 2009
North	100	2:1	37.8±10.7	Duseja et al., 2006
North	150	3:1	42.2±10.5	Bhat et al., 2006
North	25	4:1	33	Agarwal et al., 2001

Pathogenesis

Much has been learned regarding the pathogenesis of fatty liver in the last decade, till the complete pathogenesis has not been understood to the full extend. Both insulin resistance and retention of lipids within the hepatocytes are mostly implicated in pathogenesis of NAFLD. A second hit theory which is essentially a oxidative injury mechanism has also been suggested. [19]

Strong epidemiological, biochemical, and therapeutic evidence support the premise that the primary pathophysiological derangement, in most patients with

NAFLD, is insulin resistance. Insulin resistance leads to increased lipolysis, triglyceride synthesis, increased hepatic uptake of free fatty acids, and accumulation of hepatic triglyceride. Several fat derived hormones, such as adiponectin, leptin, and resistin, are important regulators of hepatic insulin sensitivity. At the cellular level, these effects appear to be modulated through altered activation of numerous receptors, membrane glycoproteins, and cytokines. Factors that determine the presence and extent of necroinflammation are not yet well understood.[20]Sseveral possible mechanisms have been theorized, including host factors, such as defects in mitochondrial structure and function, impaired free oxygen radical scavengeing, increased hepatic iron, and hepatotoxic byproducts of intestinal bacteria.[21] Activation of both lobular stellate cells and hepatic progenitor cells have been observed in NAFLD. [20, 21, 22,23]

Clinical Features and Natural course of the disease

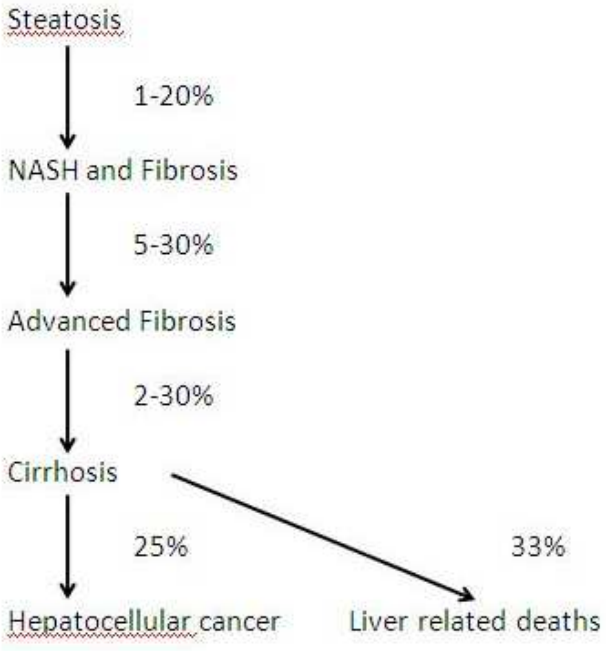
Majority of NAFLD cases are diagnosed radiologically during health screening or unrelated issues. Few cases are diagnosed while evaluations are being undertaken for altered liver function tests. So a vast majority of the patients can be asymptomatic. If present, the commonest symptoms include fatigue, malaise and right upper quadrant discomfort, and mild jaundice. Hepatomegaly is also a frequent finding on clinical examination. It has been reported upto 75% of patients, but these findings do vary a lot. [24]

Table: 3.4 Primary Presentation of 100 Consecutive cases of Incidentally Detected NAFLD. [24 25]

Primary Representation	Number of Patients
Non-ulcer Dyspepsia	43
Irritable bowel syndrome	29
GERD	7
Peptic ulcer	6
Intestinal tuberculosis	3
Functional abdominal pain	3
No symptoms (asymptomatic spouses of NAFLD patients)	2
Biliary colic	1
Elevated transaminase	3
HBV carrier	3

The natural history of NAFLD is quiet variable. A predicted evolution based on the current data is decapitated on figure given below.

Figure 3.2 Natural History of NAFLD



A population based study showed only a slightly lower survival rates than general population.[26] Increasing age, Glucose intolerance and existence of cirrhosis were associated with increased mortality.

In patients with simple steatosis, progression to cirrhosis may occur in 4%-5% over a period of 8-15 years, while steatohepatitis progress in over 25% patients over the same period.[27] At initial biopsy 5-25% of patients with NAFLD may have cirrhosis. Once cirrhosis develops the cumulative probability of complications and need for transplantation and mortality is same as hepatitis C related cirrhosis.[28]

Pathology

The major histological features of NAFLD resemble those of alcohol-induced liver disease and include steatosis, steatohepatitis (parenchymal inflammation with or without accompanying focal necrosis), and varying degrees of fibrosis, including cirrhosis. [30] Steatosis is predominantly macrovesicular and usually is distributed diffusely throughout the liver lobule, although prominent microvesicular steatosis and zone 3 (perivenular) steatosis have been reported occasionally. Mild lymphocytic, neutrophilic, or mixed inflammatory infiltrates also may be observed, and glycogenated nuclei are common. NASH, which is an advanced form of NAFLD, is indistinguishable histologically from alcoholic hepatitis. [31] Steatosis is present in all cases and can affect the hepatic lobules either diffusely or primarily in the central zones. The intensity of the inflammation varies with the severity of

steatohepatitis and may be milder in NASH than in alcoholic hepatitis. [31] Glycogenated nuclei may be present. Hepatocyte ballooning and hepatocyte necrosis of varying degrees often are present and may portend a worse prognosis. [32, 33] Mallory (or Mallory-Denk) bodies, which may be small, sparse, and inconspicuous, are seen frequently. Mild stainable iron may be present in up to 50% of the patients. Pericellular, perisinusoidal, and periportal fibrosis has been described in 37% to 84% of patients with NASH. The extent of fibrosis varies considerably, ranging from delicate strands surrounding small veins or groups of cells to densely fibrotic septa with distortion of the hepatic architecture [32]The Pathology Committee of the NASH Clinical Research Network and several other bodies have designed and validated a histological feature scoring system that addresses the full spectrum of lesions of NAFLD and proposed a NAFLD activity score (NAS) for use in clinical trials [33 34]

Table 3.5 Scoring system for NASH

Necro-inflammatory Grading	
Grade 1 (Mild)	Steatosis (mainly macrovesicular) involving up to 66% of lobules; occasional ballooned perivenular hepatocytes; scattered neutrophils; with or without

	lymphocytes; no or mild chronic portal inflammation.
Grade 2 (Moderate)	Steatosis of any degree; obvious ballooning; intralobular neutrophilis; perivenular pericellular fibrosis; mild to moderate portal and intralobular chronic inflammation.
Grade 3 (Severe)	Panlobular steatosis; prominent ballooning and disarray; marked lobular inflammation, neutrophil and lymphocyte pattern similar to grade 2.
Fibrosis Staging	
Stage 1	Pericellular fibrosis, perivenular areas. Focal or extensive
Stage 2	As above, plus focal or extensive periportal fibrosis
Stage 3	Bridging fibrosis, focal or extensive
Stage 4	Cirrhosis

Metabolic Syndrome and Fatty Liver

The term metabolic syndrome refers to a constellation of the risk factors if present together have been reported to increase the risk of cardiovascular disease. The most common accepted definitions of MS as of today are those set out by the International Diabetes Federation, the WHO, and the National Cholesterol Education Program – Adult Treatment Panel – III (ATP III) recommendation. The ATP III recommendations are detailed in Table 3.6[29]

The main pathophysiological mechanisms in metabolic syndrome are insulin resistance and obesity. Various guidelines are formed in view of the above factors. Treatment history for hypertension, diabetes or dyslipidemia is a also taken into consideration even when the investigatory parameters and clinical examination is normal.

The pathophysiological mechanism – insulin resistance and excess circulating free fatty acids are both common to metabolic syndrome and fatty liver. Some authorities have termed fatty liver as the “hepatic component of Metabolic syndrome” [36] The risk factors for the development of NASH were identified as those related to metabolic disorders, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. By the late 1990s, NASH was conceptualized as part of the metabolic syndrome.

Table 3.6 Definition of Metabolic Syndrome according to Modifiied ATP –III criteria (2004)

Risk Factors	**Modified ATP –III criteria (2004)**
Obesity (BMI)	Not used for diagnosis
Abdominal obesity	Waist circumference M: ≥ 90cm, F: ≥80cm * *for Asian population*
Blood Pressure	Systolic: ≥ 130 and/or Diastolic: ≥ 85 mmHg or on medication
Fasting plasma glucose	≥ 100mg/dL (6.1 mmol/L) or on medication for diabetes
Micro-albuminuria	Not used for diagnosis
Triglycerides	≥ 150 mg/dL (1.7 mmol/L)
HDL Cholesterol	M: <40mg/dL (1.04 mmol/L), F: <50 mg/dL (1.3 mmol/L)
Metabolic syndrome definition	At least any three risk factors

Though it looks theoretically attractive to call NAFLD as hepatic component of metabolic syndrome, a lot need to understand regarding fatty liver pathogenesis and physiology before this is being put into practice.[37, 38]

Diagnosis -

Labortary Studies. [41 42]

Mild to moderate elevation of AST and ALT can be present in cases of NAFLD and more so in cases of NASH. The AST/ALT ratio is generally less than one. The AST and ALT values can be anywhere between 1.5 to 4 times the upper limit of normal. Very high (x10times or more) elevation of AST and ALT should raise the suspicion of alternate diagnosis. The serum ALT level usually is greater than the AST level, in contrast with the pattern of alcoholic hepatitis, in which the AST level is at least twofold higher than the ALT level. The serum levels of alkaline phosphatase may be also elevated in cases of NAFLD. But other liver function values tend to be normal unless there is associated cirrhosis or hepatic dysfunction. [36] Some patients, in some studies upto 25% of NAFLD population was associated with low positive titers of ANA (Anti nuclear antibodies) Increased Ferritin levels, elevated transferrin saturation, autoantibodies, hypoalbubinemia, prolonged prothrombin time etc can be associated with NAFLD. Viral serology, mostly for Hepatits B and C infections, serum Alfa protein levels and ceruloplasmin levels should also be measured as a part of evaluation [39,40]

Imaging

Ultrasound is the most commonly used modality for detection of hepatic steatosis. On USG fatty liver is seen as a bright liver with echogenicity of liver more than right kidney. Overall USG has a sensitivity of 60%-90% and specificity of 84%-95% for detecting fat, but combined fat and fibrosis can show hyper echoic lesion in liver up to 98.7% of patients, known as fibrofatty pattern . The USG pattern can be focal or diffuse. Diffuse steatosis may be of three types [41]

1. Mild: Minimal diffuse increase in hepatic echogenicity, normal visualization of diaphragm and intrahepatic vessel borders.
2. Moderate : Moderate increase in hepatic echogenicity , slightly impaired visualisation of intrhepatic vessels and diaphragm
3. Severe : marked increase in echogenicity, poor penetration of the posterior segment of right lobe of love and poor or non visualization of the hepatic vessels and diaphragm

Contrast ultrasound has been used to pick up fibrosis and differentiate patients of NASH and NAFLD. Focal fat may show rapid change with time both in appearance and resolution, it does not alter the course or caliber of regional blood vessels and does not produce contour abnormalities. Sometimes focal fat may produce geographic map-like boundaries.

CT Scan Normal attenuation of liver is between 50 and 75 HU and is more than the spleen by 4-8 HU. As liver gets fatty its attenuation decreases and may become less than that of the spleen with a difference up to 10HU or less. Liver attenuation decreases by 1.6HU/mg of Triglyceride deposited per gram of liver tissue. In patients with severe steatosis attenuation of liver is less than blood in portal and hepatic veins. Data from the transplant donors have shown that non contrast CT is helpful in detecting steatosis of 330% or more with 100% specificity and 82% sensitivity. CECT can be used to quantify the amount and degree of steatosis. [42]

MRI – Magnetic resonance imaging is the most accurate non invasive modalities available technique for detection and quantification of hepatic steatosis. Chemical Shift MRI and MR Spectroscopy offers added advantage fatty liver imaging in terms of better sensitivity and with its ability to delineate steatosis and fibrosis

Fibroscan - Fibroscan is based on one dimensional elstography and used both USG and low frequency elastic (50) HZ waves to measure the liver stiffness. It has the ability to detect fibrosis in addition to fatty liver.

Liver Biopsy - Liver biopsy is the gold standard for diagnosis of NASH and fibrosis. Liver biopsy is the only diagnostic test that can reliably quantify hepatic steatosis, necrosis, and fibrosis; and the histologic stage of NAFLD and biopsy finding is the best prognostic indicator. But being an invasive procedure the role of liver biopsy in establishing the diagnosis of NAFLD has been debated. Potential

complications, limited therapeutic options even after diagnosis, the cost and time consumed etc make liver biopsy a less favored option among clinicians. However selected cases do warrant histopathological examination. The correlation among clinical, laboratory, and histologic findings in NAFLD is poor, and patients with normal liver biochemical test results can have significant liver injury on biopsy specimens; So in case of doubt or doubtful diagnosis, in cases assessing the prognosis is important, liver biopsy may be the answer. [47]

Non Invasive Methods [43]

Although percutaneous liver biopsy remains the gold standard for the diagnosis of NAFLD, the procedure is costly, time consuming and with some complications. The more and more cases being diagnosed as fatty liver and the search for non invasive methods has led to the development of non invasive methods to asses fatty liver and fibrosis.

Using varying combinations of indirect markers scoring systems have been developed and evaluated to estimate the extent of liver fibrosis and its aggravating factors in steatosis, and NASH, These tests include FibroTest, and NashTest, FibroMax (Biopredicive, Paris France).

The Fibro Test also called FibroSure in some countries, is the most studied and anlaysed among the above said noninvasive tests. The panel of blood tests used to estimate hepatic fibrosis includes serum α_2-macroglobulin, apolipoprotein

A-1, haptoglobin, total bilirubin, and GGTP levels, and the necroinflammatory activity index combines the same five markers plus the serum ALT level. In a study of 167 patients with NAFLD, FibroTest was highly sensitive for detecting bridging fibrosis and cirrhosis. FibroTest cutoff value of .70 had a positive predictive value of 73% and a specificity of 98% for advanced fibrosis. A cutoff value of 0.30 had a negative predictive value of 90% for advanced fibrosis. Unfortunately, 33% of patients had a FibroTest score between 0.30 and 0.70, and in this range, the test is inaccurate for assessing the stage of fibrosis. Therefore, patients with a score in this range would need a liver biopsy for accurate staging. It must be emphasized that hepatic fibrogenesis is a dynamic process, and most of the tests available are more relevant for determining the rate of fibrosis progression or response to treatment than to assess fibrosis at a particular point in time. One or more noninvasive indices of fibrosis is likely to be validated in the future and may supplant the need for liver biopsy in many, but not for all patients with NAFLD.[44,45]

Assessment of NAFLD [29]

- Careful history: particularly history of alcohol consumption
- Anthropometry: to find out the height, weight, BMI and waist circumference
- Blood pressure measurement

- Biochemical tests: serum bilirubin, serum AST, ALT, Gamma GT, albumin, globulin, fasting sugar, fasting lipid profile.
- Hematological tests: complete blood count, platelet count
- Serological and immunological tests: Anti-HCV, HBsAg, Hepatitis B core antibody. ANA, ASMA, Anti-LKM, AMA as clinically indicated
- Metabolic tests: serum ceruloplasmin, serum ferritin as clinically indicated
- Insulin sensitivity: fasting blood glucose, serum insulin fasting
- Abdominal ultrasound: with particular reference to liver echogenicity and its comparison with echogenicity of kidney and spleen vascular blurring and deep attenuation of ultrasound signal.
- Optional tests: abdominal CT scan, liver biopsy, biomarkers for liver fibrosis

Treatment of NAFLD

There is no single therapy for NAFLD. The treatment includes a multitude of approaches targeting the pathophysiological mechanisms [51]

- The metabolic associations like diabetes, dyslipidemia , obesity and hypertension
- Improving insulin resistance by weight loss, exercise or pharmacotherapy
- Hepatoprotective agents such as antioxidants to protect the liver from secondary insults

Lifestyle changes are the proven, mainstay and cost effective interventions target at NAFLD. But adherence and motivation to continue the changes lifelong remains an issue. Studies have shown that moderate amount of weight loss and exercises are associated with improvement in insulin sensitivity. A targeted weight loss of 7-10% of the baseline weight reduction in 6-12 months should be the initial goal. The weight loss should be achieved gradual and sustained manner. [52]

The optimal die to treat NAFLD is not known, however patients with NAFLD seem more likely to have a diet high in saturated fats and cholesterol and low in fiber and antioxidants. Mono and poly unsaturated fats may potentially improve insulin resistance and may be beneficial in improving hepatic steatosis.

Associated metabolic abnormalities have to be treated according to guidelines. A definitive improvement in the liver histology and a reduction in cardiovascular mortality can be expected if diabetes, hypertension and dylipidemia are adequately treated and well controlled. Among the anti obesity drugs, orlistat shows some promise. A small pilot study by Harrison et al showed improvement in aminotransferases with a mean 10kg reduction weight after a treatment with Orlistat for 6 months.

As insulin resistance is a key factor in pathogenesis of NAFLD people have used insulin sensitizers for the treatment of NAFLD. Biguanides and

thiozolidinediones are the two class of insulin sensitizers studied in human with proven results. Liver histology also shows improvement after treatment.

Hepatoprotective agents and antioxidants being studied include VitaminE, Urosodeoxycholic acid (UDCA), pentoxyphylline, betaine, probucol, silymarin and iron depletion agents. Most of the studies are in Phase 2 or 3 clinical trials and outcomes are awaited. [53]

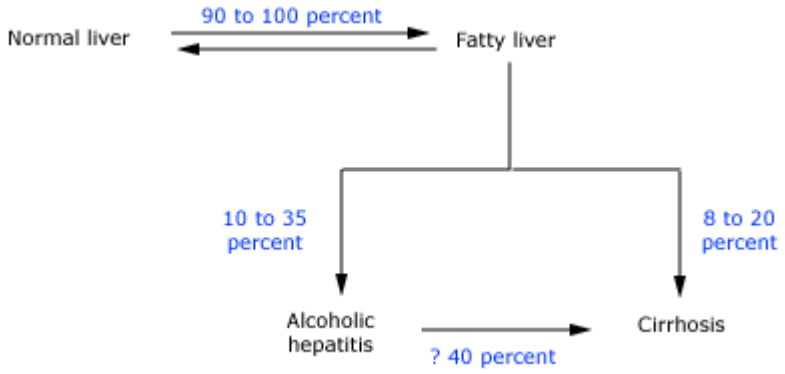
Alcohol Related Fatty liver

Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption. Alcoholic fatty liver (steatosis) is rarely diagnosed clinically because most patients are not symptomatic and usually do no seek medical attention. However, up to 90 percent of alcoholics have steatosis. Reports are available describing the development of fatty liver even with hours of alcohol binge. Fatty liver, in general represents the direct toxic effects of ethanol, in alcoholics. Population derived studies have documented in the literature that men usually must drink 40g to 80 g of alcohol daily and women 20g to 40 g daily for an average of 10 years to achieve a significant risk of liver disease. And duration shorter than this can cause fatty liver changes rather than full blown cirrhosis. [54]

Alcoholic fatty liver may be suspected in patients with a compatible history who have a suggestion of fatty liver on imaging tests or are found to have steatosis on liver biopsy. Liver tests are generally normal or modestly elevated, and jaundice is unusual. The diagnosis is established after excluding other causes of fatty liver.

The progression of liver damage is shown in the following figure.3.3 But it might be taken into account that, individual variation do occur considerably.

Figure 3.3 Progression in Alcoholic liver disease [54]



Chronic alcohol abuse can result in a spectrum of liver injury that ranges from mild fatty infiltration to cirrhosis and hepatocellular carcinoma. Fat accumulation in liver cells, which is the earliest and most predictable response to alcohol ingestion, is seen in 90% of heavy drinkers. Although fatty liver generally is a benign condition that usually reverses quickly with abstinence, cirrhosis can develop within five years in 10% of patients who continue to drink heavily.[55]

The histological picture is almost similar are described earlier for NFLD. Characteristic features include liver necrosis, mallory bodies, Infiltration by neutrophils , perivenular distribution of inflammation etc. Other nonessential histologic features include bridging necrosis, fatty changes, bile duct proliferation, cholestasis, and perivenular fibrosis. The presence of neutrophils is a hallmark of alcoholic hepatitis. [34,35]

In short fatty changes in a chronic alcoholic suggest that the process is of a shorter duration than needed for cirrhosis. The hallmark of this stage is that it is reversible, and it provides a potential opportunity to prevent cirrhosis and malignant transformation in future

High Sensitivity C - reactive protein

CRP is an acute phase reactant secreted by hepatocytes under the influence of acute inflammatory cytokines such as IL-1,IL-6 and TNF. Inflammatory markers can be used as a guideline for detecting underlying atherogenesis as well for recurrence in underlying atherogenesis. [56]

Whether CRP is just a causal component of the atherosclerotic process or a factor involved in the process is an unsolved question. Evidence is mounting that it

is not causal. The following observations are strongly in favor that CRP may have a direct role in the atherosclerotic disease causation and progression [57]

- CRP has been detected in atherosclerotic lesions.
- CRP binds to LDL, allowing LDL to be taken up by macrophages without the need for modification
- Recombinant human CRP was infused into seven normal men in whom very high serum CRP concentrations were attained (mean 23.9 mg/L). The CRP infusion was associated with marked elevations in markers of both inflammation (IL-6, IL-8, and serum amyloid A) and coagulation (von Willebrand factor antigen, prothrombin F1±2, D-dimer, and plasminogen activator inhibitor type 1).
- In an animal model of increased atherosclerosis, treatment with native CRP increased aortic plaque area.
- CRP induces adhesion molecule expression and the production of interleukin-6 and monocyte chemoattractant protein-1 (MCP-1) in human endothelial cells; these effects might enhance a local inflammatory response within the atherosclerotic plaque by the recruitment of monocytes and lymphocytes.

Rat models of myocardial infarction have shown in a study conducted by johnson etal in 2007 that CRP inhibitors would decrease the infarct size and that

effect could be blocked by a synthetic small molecule inhibitor of CRP. CRP induced complement activation is one of the central pathogenesis pathway of myocardial infarction and thus inhibitors binding to CRP blocking this effect has a use beyond doubt. In a stable coronary artery disease patient CRP levels correlate mostly with the risk of plaque rupture and the extent of underlying atherogenesis. [57]

CRP as a predictor of progression of CAD has attracted worldwide attention. In a study conducted in Belgium in 2009 it was found out that elevated CRP levels were associated with inducible ischemic changes on stress testing. This study threw light on the fact that CRP levels could be used as a tool in angina patients who were at risk for ACS in the future. It was found that CRP, SAA, IL-6 were indicative of the hyper responsiveness of the inflammatory system to small amount of stimulus thus underlying its importance. CRP at a higher level was associated with increased plaque vulnerability and more strongly associated with STEMI than NSTEMI. CRP has also been proven to be an indicator of recurrent ischemia risk after CABG. Elevated pre procedural levels are associated with poor outcome.

In the famous VAL HEFT TRIAL OF 2008 median levels of CRP were found to be higher in patients with heart failure when compared to normal population. CRP levels and sudden cardiac death however didn’t have any such direct association.

CRP was also a predictor of transplant coagulopathy and allograft failure in post cardiac transplant patients. An inflammatory process may trigger AF in patients post cardiac transplant and hence CRP could be a useful marker.

In the famous Women's health study in USA conducted in 20,000 females it was proven that CRP is an independent predictor for the risk of developing hypertension in future.

Traditional methods for measuring serum CRP were developed for use in patients with infectious and inflammatory disorders. These assays typically have a detection limit that in the range of 3 to 5 mg/L, which is above the concentration observed in most apparently healthy individuals. High sensitivity methods for measurement of CRP (hs-CRP) detect concentrations down to 0.3 mg/L. The assays are necessary for cardiovascular risk stratification, which is based upon discrimination of CRP levels extending below 3 mg/L. [59]

According to the centre for disease control and prevention and the American Heart Association a value of <1, 1-3 and >3 were given as low average and high values. A value of >10 should make us search for other markers of infection or inflammation and a value of >5mg/dl should be interpreted with caution. [58]

CRP levels in patients with Fatty liver are not studied extensively. Available studies have found increased level of CRP in these patients, and a

positive correlation to obesity, age, hypertension, and diabetes. Patients with steatoheaptitis have higher CRP levels than patients with steatosis alone. CRP is produced from liver and since the risk factors for CAD are often associations of fatty liver disease. More over increased CRP levels are reported in patients with metabolic syndrome and chronic liver disease. These factors suggest that a study of CRP levels in fatty liver disease can be of potential benefits in various ways.[60]

4.Material and Methods

Inclusion Criteria

Patients belonging to both sexes with age above 14 yrs who are otherwise asymptomatic detected to have Fatty liver in Ultrasonogram.

Exclusion Criteria

1. Symptomatic patients – Patients with short term or long term symptoms corresponding to any organ systems.
2. Patients with any preexisting chronic illness or concurrent illness.
3. Patients with any kind of drug intake.
4. Known patients of Acute or Chronic Liver disease of any etiology.
5. Patients with recent (<4wks) history of starvation or prolonged fasting.
6. History of Gastro Intestinal Surgery or recent surgery (<3 months)
7. Patients with an hsCRP value of 5mg/L or more *

*Since a value more than 5 mg/L denotes an acute inflammation, infection, trauma or surgery.

The study population was derived from patients and general public attending the Master Health Checkup of Stanley Medical College, Chennai from December 2010 – November 2011

Fatty liver was diagnosed by Ultrasonogram, which was done by a Radiologist. All the images were reviewed by another radiologist to minimize observer error. The presence of fatty liver was graded from mild to severe. For all practical purpose it was taken present or absent. A Lasen &Toubro Ultrasound machine with a 3.5 MHz probe was used.

After obtaining a written informed consent in the native language, a detailed inquiry was made into the history to rule out any clinical symptoms or significant past medical illness. History of surgeries in the past and medications were also enquired about. In addition women were enquired about oral contraceptives or hormonal use. History, duration and amount of alcohol consumption was also recorded. The presence or absence of alcohol intake was then independently confirmed by a family member of the patient. In selected cases psychiatric counselors help was obtained.

After getting the history and relevant details, a thorough physical examination was done for the selected group. Vitals including pulse and blood pressure were recorded. Anthropometric measurements – weight, height, and waist circumference were measured. Waist circumference is measured with patient

stripped or when it's not acceptable, with the patient wearing very light clothes. Adequate precautions were taken to minimize any potential errors. BMI is calculated as per the formula weight in kilograms divided by meter square. Patients were classified into 4 groups according to the calculated BMI

Underweight: BMI <18.5 kg/m2

Normal weight: BMI 18.5 to 24.9 kg/m2

Overweight: BMI 25 to 29.9 kg/m2

Obese : BMI > 30 kg/m2

Blood sample was drawn for carrying the laboratory investigations. Laboratory investigations carried out includes Fasting blood sugar, after an overnight fasting of 8 hours, Liver function tests – Total bilurubin, AST, ALT and Alkaline Phosphatase, Lipid Profile which includes Total cholesterol, Triglycerides, HDL and LDL. Plasma hs-CRP level was measured by nephalometric method using the turbox-sf analyser.

Standard Laboratory Normal Values:

AST (Normal value 5 to 35 IU/L)

ALT (Normal value 5 to 35 IU/L)

Serum Alkaline Phosphatase (Normal 44 to 147 IU/L)

Serum Total Bilirubin (Normal - < 1 mg/dl)

Research Design

This is a cross sectional study assessing the clinical and laboratory profile of patients diagnosed with Fatty liver by radiology screening and assessing the serum levels of hsCRP

Statistical Analysis

Statistical analysis of the data obtained from the study was done using the ‘z’ test or ‘normal’ test to compare the mean values of two groups of participants. Fishers exact test was also used when appropriate. The calculations were done for 5% level of significance (P = 0.05). Pearson product-moment correlation coefficient was used to find the correlation between hsCRP and other variables. Statistical analysis was carried out using Microsoft Excel ® and SSPS Software for predictive analysis from IBM ®.

5.RESULTS AND OBSERVATIONS

In this study a total of 67 patients were included, after applying the exclusion criteria. Most of them presented to the Master Health Checkup Clinic and were found to have fatty liver during USG screening.

There were 41 (61%) female and 26 (39%) male patients.

The mean ages of the participants were 48 ± 12.5 years. Majority of the patients, (40) belonged to 31 - 50 age group.

Anthropometric characteristics

The anthropometric characteristics measured include Weight, Height, and Waist circumference. Mean values obtained are given in the table below. P values were determined using student t test.

Table 5.1 Anthropometric characteristics of males and females

	Male	Female	P value
Weight (kg)	72.23±12.36	67.4±13.25	0.14
Waist Circumference (cm)	85.73±11.58	83.7±12.61	0.51
BMI (kg/m2)	26.79±4.54	26.7±5.02	0.95

Figure 5.1 – Sex distribution Pie chart

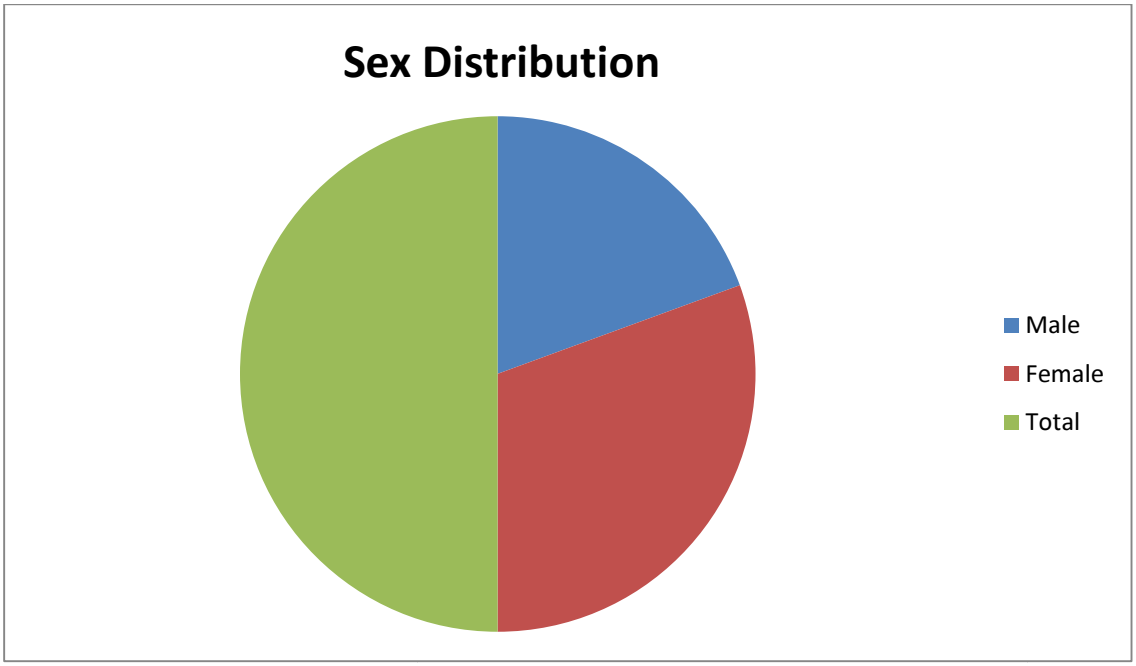
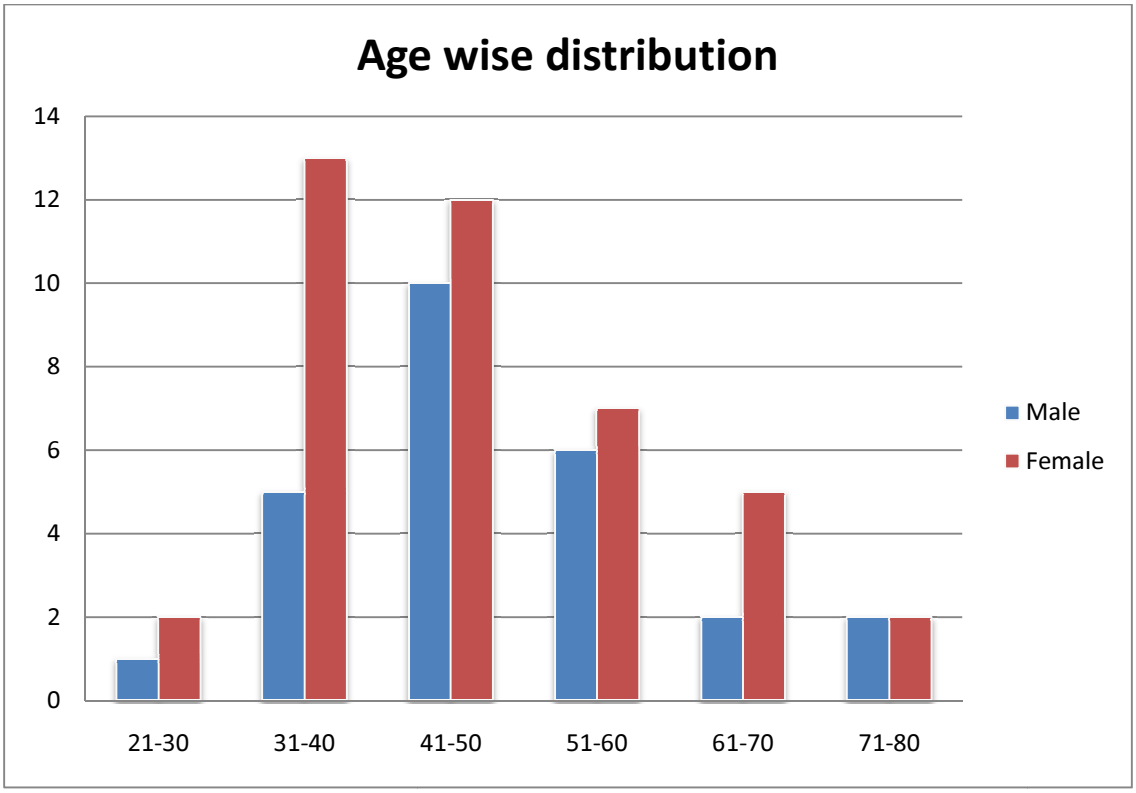


Figure 5.2 – Age Distribution Bar Diagram



The mean weight of male population was 72.2±12.4 kg and that for female population was 67.4±13.3. kg Waist circumference of male population was 85.73±11.58 in cm and females 83.7±12.61 in cm. There was no statistical difference in any of the measured values between males and females.

Waist Circumference

Data regarding the waist circumference is given below. 17 males and 19 females had increased waist circumference, according to the ATP III criteria.

Table 5.2 Waist Circumference Males and Females

Waist circumference(males)	Number	Percentage (%)
<90 cm	17	65.4
>=90 cm	9	34.6

Waist circumference(females)	Number	Percentage (%)
<80 cm	19	46.3
>=80 cm	22	53.7

BMI

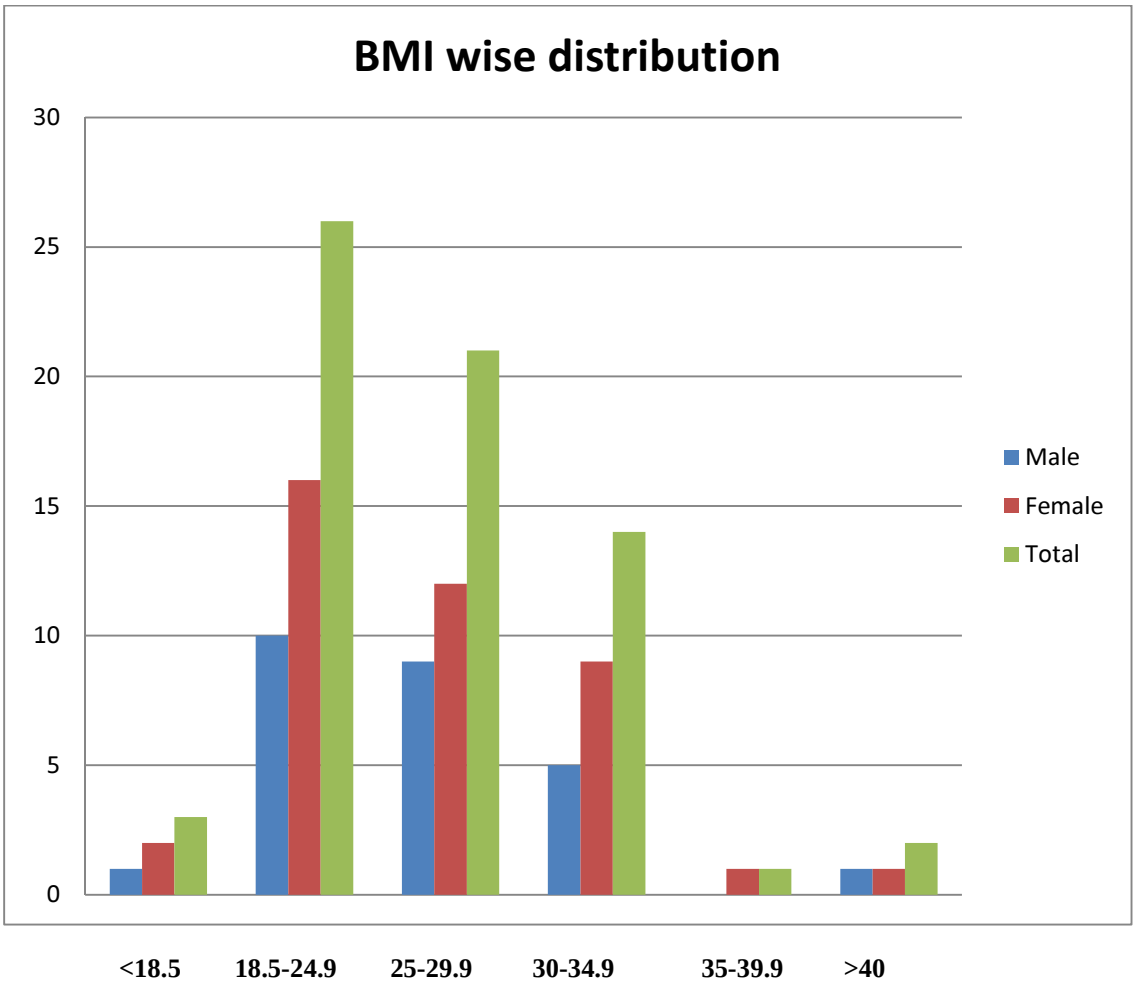
BMI is calculated from the weight and height as per the formula BMI = Weight in Kg/ (Height in meter)^2. The population was then further classified into normal, overweight, obese class 1, class 2 and class 3 according to the BMI. The BMI value for males was 26.79±4.54 and for females was 26.7±5.02. The following table gives the results obtained.

Table 5.3 BMI classes of the study population

BMI (kg/m^2)	Male	Female	Total
<18.5 Underweight	1	2	3
18.5-25 Normal	10	16	26
25-29.9 Over weight	9	12	21
30-34.9 Obese - Class1	5	9	14
35-39.9 Obese – Class 2	0	1	1
>40 Obese – Class 3	1	1	2

2 out of the 67 had morbid obesity. 26 patients had normal BMI characteristics. 21 were overweight, 14 of them were having Class 1 obesity. 1 patient had class 2 obesity. There were 3 patients, one male and 2 female who were having underweight according to the BMI class.

Figure 5.3 BMI wise distribution of the study population



Clinical Characteristics

There were 6 patients with clinically significant alcohol intake. This constitutes 8.9% of the whole population. Enlarged liver was noted in 6 patients (8.9%). Viral serology for hepatitis – Hepatitis B and C were negative for all the 67 patients.

Table 5.4 Clinical characteristics of the population

Significant Alcohol Intake	6(8.9%)
Hepatomegaly	6(8.9%)
Positive viral Marker HbsAg, anti HCV	Nil

Blood Pressure

The mean systolic and diastolic blood pressures are 129.7 and 85.3 millimeters of mercury. There is no statistically significant difference in blood pressure among the male and female populations.

Table 5.5 Blood pressure – Male and Female

(mmHg)	Male	Female	
BP systolic	128.3±16.1	130.6±15.	0.57
BP diastolic	85.4±12.5	85.1±11.5	0.94

Table 5.6 - Blood Pressure classes of the study subjects according to JNC7 classes

BP	Number	Percentage (%)
Normal	14	20.8
Pre Hypertension	35	52.2
Stage 1 Hypertension	14	20.9
Stage 2 Hypertension	4	5.9

Laboratory values

The table below gives the comprehensive mean data of the laboratory values analysed in the study.

Table 5.7 Mean Laboratory values – Comprehensive table

Fasting Blood Sugar (mg/dl)	102 ± 38.49
Total Cholesterol (mg/dl)	213.76±45.66
Triglycerides (mg/dl)	128.01±51.37
LDL (mg/dl)	140.0±42.91
HDL (mg/dl)	48.41±10.14
Total Bilurubin (mg/dl)	1±1.02
AST (IU/L)	32.71±15.34
ALT (IU/L)	32.74±22.42
ALP (IU/L)	108.6±53.2

Fasting Blood Sugar

The mean blood sugar value was 102±38.49mg/dl. Among the 67 patients studies, 19 (28%) had either newly detected impaired fasting glucose levels or diabetes mellitus.

Table 5.7 Fasting Blood Sugar values

Fasting Blood Sugar Values (mg/dl)	n	Percentage (%)
FBS <100	48	71.6
FBS 100-126	10	14.9
FBS >126	9	13.4

Lipid Profile

The mean total cholesterol was 213.76±45.66 LDL 140.0±42.91 Triglycerides 128.01±51.37 and HDL 48.41±10.14 (all values in mg/dl). The percentage of cases falling into each category of lipid levels as per the ATP III norms are given below in Table 5.8

Table 5.8 - Lipid profile of the study group according to Adult treatment panel III classification of LDL, total, and HDL cholesterol

LDL Cholesterol (mg/dl)	No. of values	Percentage (%)
LDL<100 - Optimal	12	17.9
100 to 129 - Near normal or above optimal	17	25.4
130 to 159 - Borderline high	20	29.9
160 to 189 - High	10	14.9
≥190 - Very High	8	11.9

Total cholesterol (mg/dl)	No. of values	Percentage (%)
<200 - Desirable	29	43.3
200-239 - Borderline High	20	29.9
≥240 - High	18	26.8

HDL cholesterol (Males) (mg/dl)	No. of values	Percentage (%)
<40 - Low	6	23.1
≥40 - High	20	76.9
HDL cholesterol (Females) mg/dl	No. of values	Percentage (%)
<50 - Low	21	51.2
≥50 - High	20	48.8

Liver function tests

The relevant liver functions results from the study group are given below in the tables below.

Table 5.9 Liver Function tests

	Number	Percentage
AST > 35 IU/L	20	29.8
ALT > 35 IU/L	19	28.3
ALP > 147 IU/L	10	14.9

Table 5.10 Liver fucnction tests compared in alcoholics and non alcoholics

	Alcohol Related Fatty liver	NAFLD	P value
AST	44.66+33.0	31.54+12.25	0.38
ALT	57.5+63.5	30.5+12.19	0.34
ALP	112.5+27.5	108.16+55.21	0.74

Metabolic Syndrome

The number of patients with metabolic syndrome in the study population was calculated according to the ATP III guidelines. Among the 67 patients, 19 were found to have metabolic syndrome. The data is represented in the figure .

Figure 5.4 Percentage of fatty liver patients with metabolic syndrome according the NCEP – ATP III guidelines for Asian population

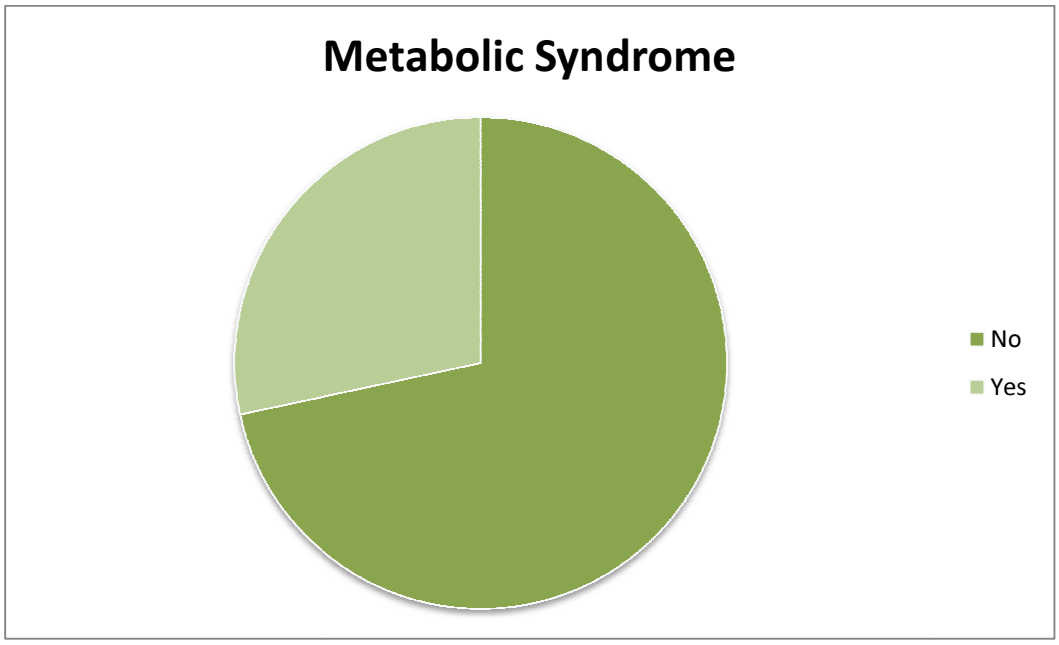
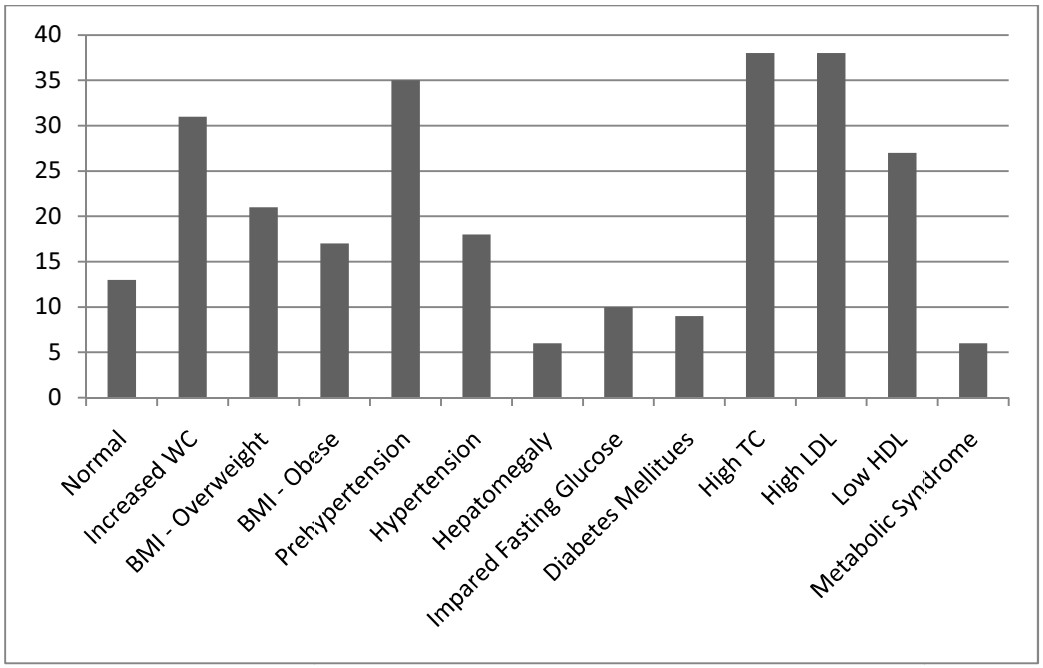


Figure 5.5 – Compilation Bar graph of clinical and laboratory abnormalities*



*Since many of the study subjects had more than one clinical or laboratory abnormalities the total from the bar graph will be more than the total study population.

High Sensitive C – Reactive Protein levels.

High Sensitive C – Reactive Protein (hsCRP) levels were measured in all the 67 patients. As indicated earlier only cases with a hsCRP levels <5mg/l only were included in study. The mean value of hsCRP level was 2.16±1.11 mg/l. The values range was from 0.48 to 4.82

The statistical characteristics of the serum levels of hsCRP are mentioned in the table given below.

Table 5.11 Statistical characteristics of hsCRP levels

Mean value	**2.1607**
Highest value	4.8200
Lowest value	0.4800
95% CI for the mean	1.8905 to 2.4310
Median	2.0800
95% CI for the median	1.7306 to 2.3298
Variance	1.2277
Standard deviation	1.1080
Relative standard deviation	0.5128 (51.28%)
Standard error of the mean	0.1354
Coefficient of Skewness	0.5931 (P=0.0455)
Coefficient of Kurtosis	-0.5229 (P=0.3087)
D'Agostino-Pearson test for Normal distribution	accept Normality (P=0.0807)

The mean values of hsCRP levels in males and females are outline below. The difference is not statistically significant.

Table 5.12 hsCRP levels comparision in males and females

	Male (n=26)	Female (n=41)	p-value
hsCRP	2.21±1.14	2.18±1.11	0.41

The mean hsCRP values in cases classified to have metabolic syndrome and with no metabolic syndrome are and respectively. The p values are less than <0.001 and henceforth the difference is highly statistically significant.

Table 5.13 hsCRP levels compared in fatty liver patients with and without metabolic syndrome

Metabolic Syndrome (n=19)	No Metabolic Syndrome (n=48)	p-value
3.12±0.99	1.79±0.92	<0.001

In patients with metabolic syndrome there was a highly significant difference in levels of high sensitive CRP levels.On comparing hsCRP levels of alcoholic and non alcoholic fatty liver case the following results were obtained.

Table 5.14 hsCRP levels compared in alcoholic and non alcoholic patients

	Alcohol related Fatty liver disease	Non alcohol related fatty liver disease	p- value
Mean hsCRP	1.96±0.58	2.18±0.92	0.64

The mean hsCRP in alcoholics were 1.96±0.58 and NAFLD group were 2.18±0.92 and there was no statistically significant difference when compared to NAFLD group, owing to the small number of alcoholic fatty liver cases in the study.

A cardiovascular risk classification of low risk (<1.0 mg/L), average risk (1.0 to 3.0 mg/L), and high risk (>3.0 mg/L) corresponding to hs-CRP in the adult population was proposed by the Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA). A risk stratification of the study group is being done according to the data as shown in the table 5.14.

Corellation of Different variables with hsCRP.

The correlation of fatty liver with hsCRP and the various clinical and laboratory values were assed using the Pearson product-moment correlation coefficient. The following results were obtained as given in table 5.15

Among the variables, Waist circumference and BMI showed moderate degree of correlation. The variable which correlates maximally is waist circumference, a correlation factor of 0.61

Blood pressure showed a weak but, positive correlation 0.3. Among the lipid profile, total cholesterol, and Triglycerides and LDL showed weak positive correlation, while HDL showed a weak negative correlation.

The correlation coefficients of liver function tests were not significant or strong.

Representative scatter diagrams for correlation variables with hsCRP levels on X axis are shown below.

Table 5.14 Cardiovascular risk stratification of the study population according to the hsCRP levels

hsCRP levels	Number	Percentage (%)
<1	7	10.4
1-3	46	68.7
>3	14	20.9

Figure 5.7 Pie chart demonstrating Cardiovascular risk stratification of the study population according to the hsCRP levels

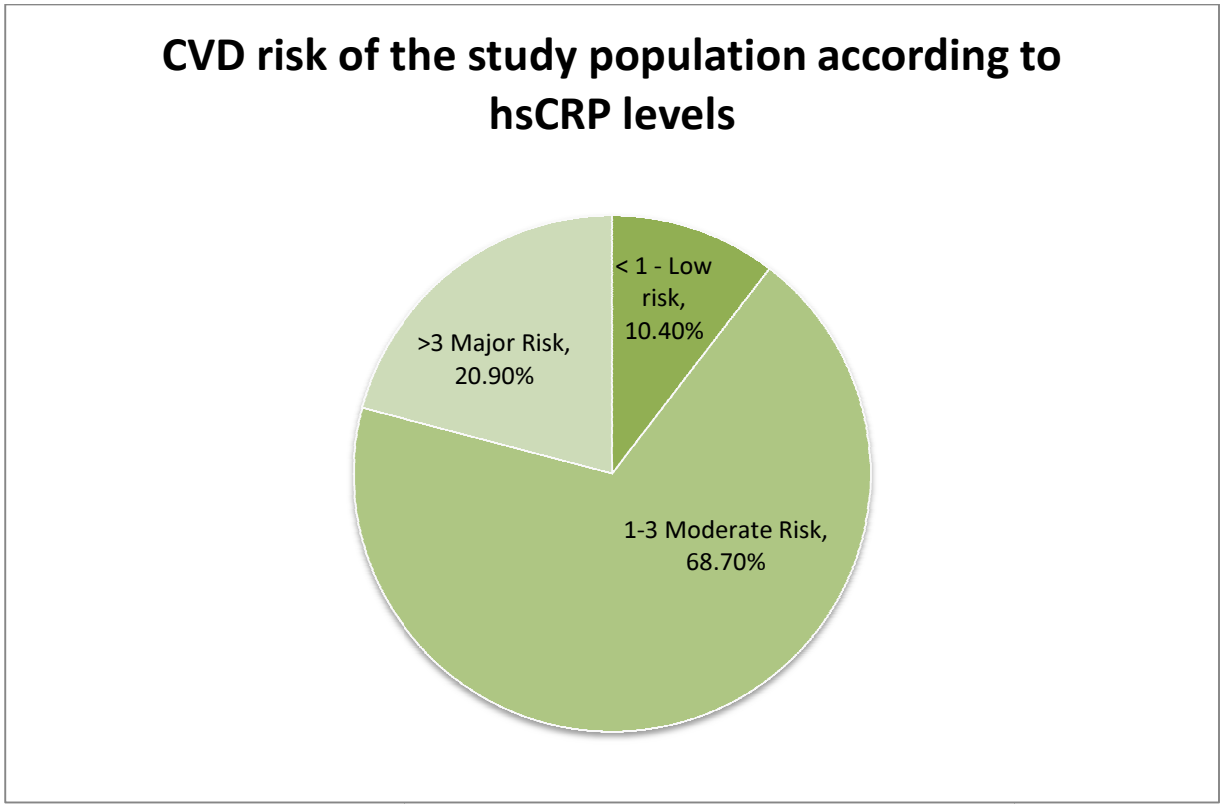


Table 5.15 – Pearsons correlation coefficient – r of hsCRP with various parameters

Factor	Correlation	p-value
Age	-0.04	0.74
Waist	0.61	<0.001
Weight	0.51	<0.001
BMI	0.48	<0.001
BP(Systolic)	0.32	0.008
BP(Diastolic)	0.31	0.010
FBS	0.06	0.620
TC	0.31	0.010
TG	0.22	0.073
HDL	-0.26	0.033
LDL	0.3	0.013
T.Br	-0.06	0.629
AST	-0.01	0.936
ALT	0.1	0.420
ALP	-0.01	0.936

Figure 5.8 Scatter plot – showing correlation between hsCRP and Waist Circumference

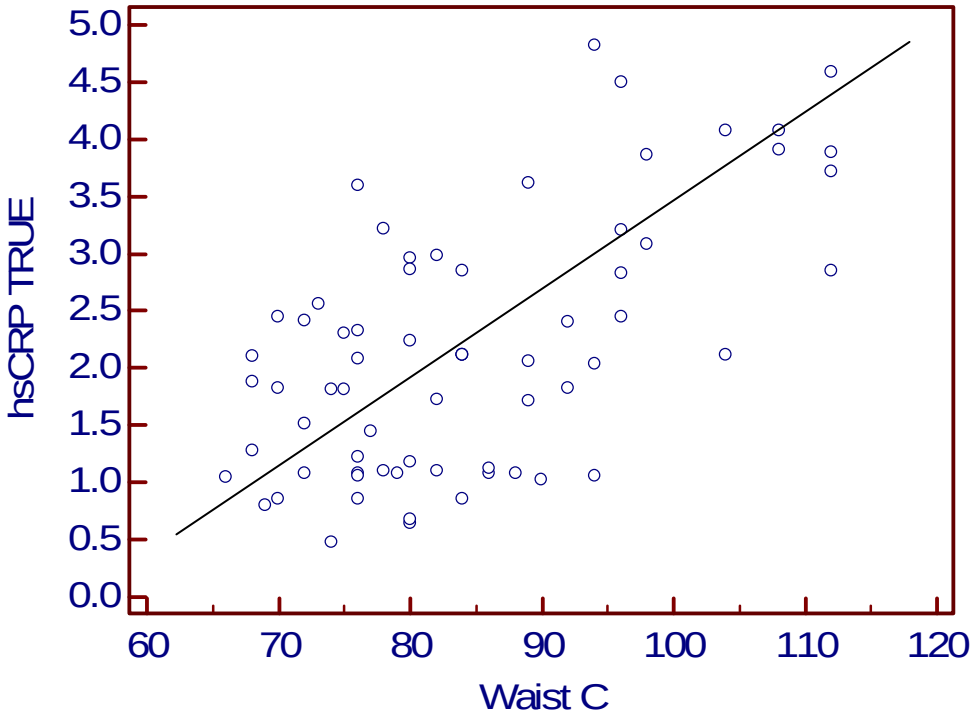


Figure 5.9Scatter plot – showing correlation between hsCRP and Waist Circumference in patients with metabolic syndrome and without metabolic syndrome.

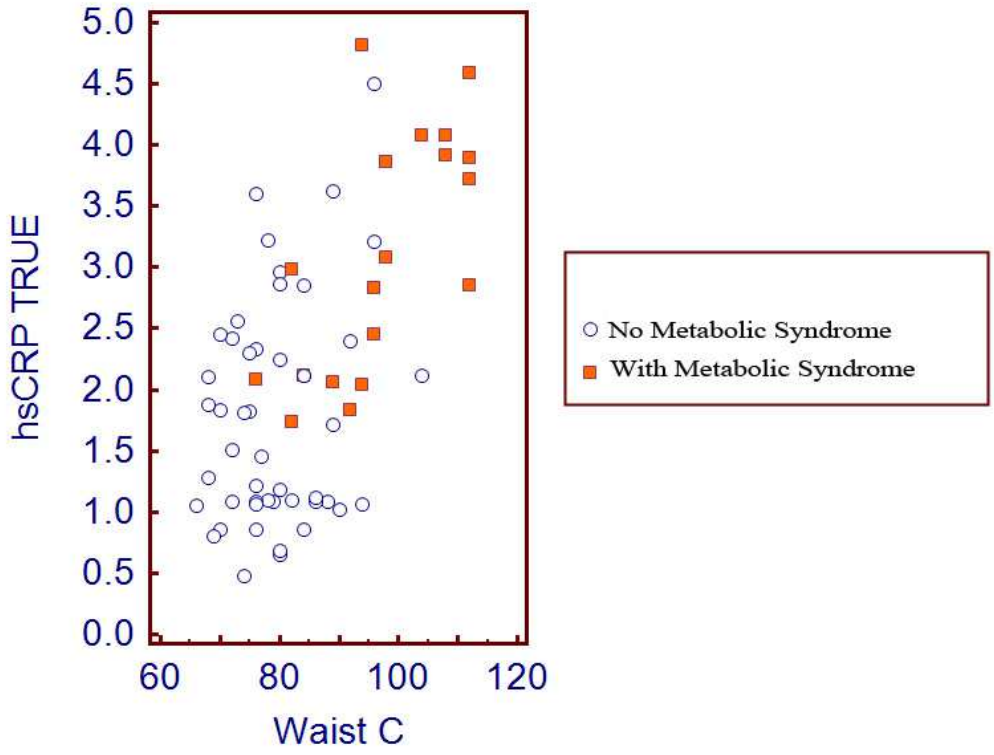
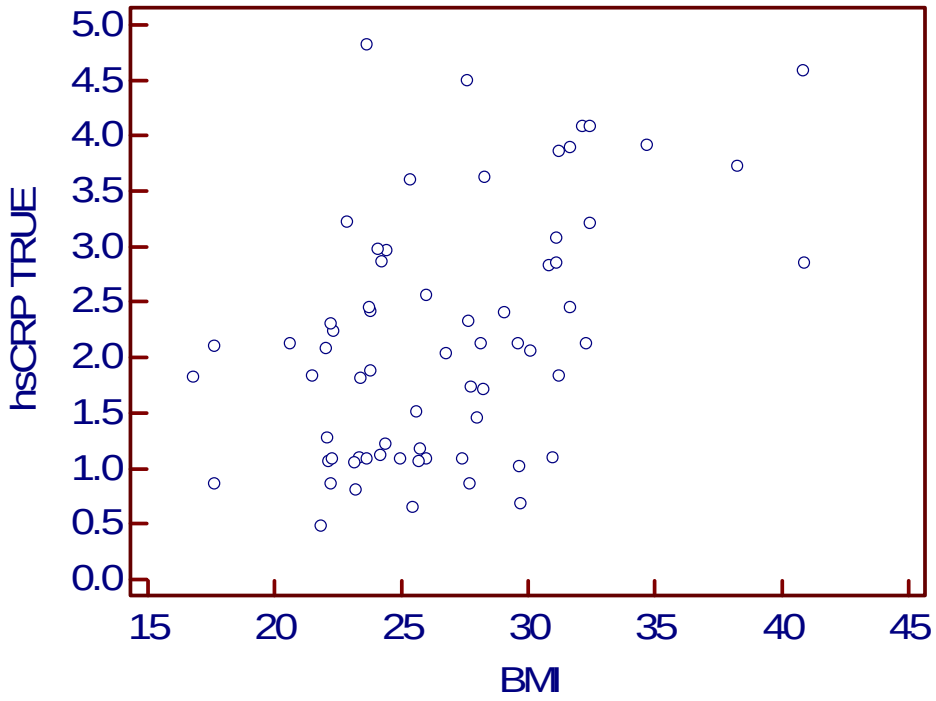


Figure 5.10 Scatter plot – showing correlation between hsCRP and BMI



6.Discussion

Demographic Profile

A total of 67 cases with included in the study after applying the exclusion criteria. Since patients with any concurrent symptom or illness or chronic illness were excluded from the study, a considerably large number of cases diagnosed with fatty liver were ruled out of the study. 12 patients, who would have qualified otherwise, had high hsCRP levels, i.e. more than 5 mg/l. A level more that 5mg/dl is considered to be representative of infection, inflammation surgery or traumatic origin and not of cardiovascular risk.[61] So these cases were excluded from the study.

In this study the predominant population was female - 61%. The mean age of the participants was 48 ± 12.5 years. Majority of the patients (40) belonged to 31-50 age group. Almost all studies from all over India reports that the proportion of males in more , if not equal. Amarapurkar et al in 2000 reportes a male to female ratio of 2:1, Bhat etal in 2006 reported a ration of 3:1 .[62,63] This of course depends on the population demographics of people attending the Master health

checkup clinic. But considering the fact that 6 male patients of alcoholic fatty liver disease is also included, this female predominance may be significant.

Anthropometric characteristics

Among the measured anthropometric characteristics, the mean BMI was 26.7±4.9. Most of the patients fell in to the class of Normal BMI n= 26 (39%) followed by Overweight- n=21 (31 %.). Many Indian studies give similar observation. A study from coastal eastern India has shown that only about 46% of NAFLD patients were either overweight or obese (meaning that more than 50% were having a normal BMI as per the WHO criteria). On the contrary, only about 22% of the patients in the studies by Uchil et al. and Duseja et al. had a normal BMI. In contrast, abnormal BMI has been documented in 40%-100% of NAFLD patients in the West. [14,15,18] So it is evident that, according to BMI values, comparatively less patients qualify to have obesity when compared to western data.

BMI classes do not take race and population characteristics into consideration. Since the Indians, especially South Indian population is known to have more visceral fat as compared to others BMI measurement may underestimate obesity and associated risks.

Waist Circumference seems more reliable in this regard. 65% of the males and 46% of females had a waist circumference above the cutoff values proposed by

the NCEP – ATP recommendations. Duseja et al reported that 72% of the male and 93% of the female population had a waist circumference that was more than the proposed cutoff (Waist circumference >90 cm in males and more than 80 cm in females). Some other Indian studies show lesser prevalence though, like Amarkpur etal observing high WC in 57% of the patients. [62, 63] But universally the waist circumference appears to be above normal in a good number of cases diagnosed with fatty liver disease.

Clinical Features and Labortaty measurements.

A total of 18 (27%) new hypertensive and 35 pre-hypertensive patients were discovered during the study. Ramachandran et al reported an age-adjusted hypertension in Chennai (South India) as 21.8% in a sample of 532 males and 421 females aged >40 years. This study included general population, not fatty liver patients. Essential hypertension is associated with the metabolic syndrome, insulin resistance and the development of fatty liver. M J Brookes and B T Cooper in Journal of Human Hypertension, states that it is important to consider the diagnosis of fatty liver disease in hypertensive patients, to measure the liver function tests at diagnosis and not to ignore minor elevations of serum aminotransferases. Considering the fact that these patients were asymptomatic, and if not for the health screening their blood pressure would not have come to the light, screening for hypertension should be strongly recommended in fatty liver patients.

The study showed that 10 0ut of the 67 (15%) of asymptomatic patients presenting with fatty liver had impaired fasting blood sugars and 9 had (13.4%) had diabetes mellitus. This is to be considered while keeping the the fact that the reported prevalence of diabetes among the general population in Chennai is 13.5%, in a study Mohan etal. [64]

Regarding diabetes mellitus other Indian studies have reported a prevalence of 12-25% .A recent study on the prevalence of NAFLD among Italian diabetic population reported a figure of 69.5%. In a study among healthy Japanese adults, the prevalence of NAFLD increased from 27% with normal fasting glucose to 43% in those with impaired fasting glucose and to 62% in subjects with newly diagnosed diabetes. In others studies from Asia pacific region, the prevalence of NAFLD among diabetic subjects was 54.5%, which is significantly higher than those found among subjects with pre-diabetes (IGT or IFG) (33%), which in turn is higher than those with normal glucose tolerance (22.5%). [65 66]

Among the 67 patients only 6 had clinically appreciable heaptomegaly. The incidence of hepatomegaly in different studies range from (Saudi series (2003) - (88%) Virginia series (1996) - (22%) Lal et al (1991) - (40%). But in our study it was only 9%. [67]

Among the liver function tests, the mean transaminase levels AST and ALT were 32.7±15.3 and 32.7±22.42 respectively . A clinically significant relationship

could not be established regarding the liver function test values obtained in the current study. Around 30% had eleveated transaminases in our study, considering cut off values for AST and ALT as 35IU/L. There is poor correlation between biochemistry, ultrasonography and histology, and the entire histological spectrum of NAFLD can be seen in individuals with normal transaminase values according to Mofrad et al, 2003. [68] Some studies have mentioned that Liver enzyme levels in NAFLD patients fluctuate, normal values being present in up to 78% of patients at any one time. When levels are elevated, the increase is mild and often restricted to one or both of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The AST:ALT ratio is usually less than 1, although it may reverse in the presence of cirrhosis. [69] The AST:ALT ratio in the study group was 0.9 Many studies have reported that Alanine aminotransferase level showed the strongest association with fatty liver, a finding that is not surprising because this is a commonly used method to detect NAFLD in the general population.[70] But such an association could not be found out in our study. Amino-transferase levels are commonly used in clinical practice to estimate liver inflammation, but the use of ALT level as a reliable indicator of the severity in NAFLD is controversial as aminotransferase levels may vary from normal levels in more than two-thirds of NASH patients at any given time. [68, 69, 70] We found that among subjects with fatty liver at ultrasound, those with normal and abnormal ALT levels were very similar,

providing indirect evidence that ALT is not sorting out different conditions or stages of the disease. The mean alkaline phosphatase levels were 108.6±53.2.

There was plenty of lipid abnormalities in the study population. 26% had total cholesterol more than 240 mg/dl. 8 out of 67 (12%) had a LDL value greater than 190 mg/dl. A total of 38 among the 67 had LDL values greater than 130 mg/dl. 27 had abnormal (low) HDL values. The Framingham Heart study found higher triglycerides, and lower high-density lipoprotein (HDL) and adiponectin levels in patients with fatty liver. Subsequent research from all over the world confirmed it.[71]

Alcohol Related Fatty Liver

Alcohol consumption was enquired in the history and a total of 6 patients gave the history of significant alcohol consumption. All the 6 were males, and in good health. There were no clinical features of chronic liver diseases and not much dearrangement of liver functions except for one patient who had slightly elevated bilurubin and transaminase level. The patients with alcohol related fatty liver disease tend to be of normal weight and BMI and without much of other anomalies. However the number of patients with alcohol related (n=6) was not large enough to make any statistically significant conclusions.

Metabolic syndrome

Metabolic syndrome was detected in 19, ie 28% of the patients with fatty liver. If only patients with NAFLD are taken into consideration then it comes to 31 %. [33] The relationship between NAFLD and metabolic syndrome is becoming increasingly recognized. Lizardi-Cervera J et al from Spain reports that of 22 % of adults with NAFLD has metabolic syndrome. Various studies by Hellen Kang etal, Sameul et al and others has found out that prevalence of metabolic syndrome as 18-40%. Atleast one component of metabolic syndrome may be present in 90% of the NAFLD population. But it is still unclear whether NAFLD can be called as the hepatic component of metabolic syndrome, considering only less than one by third among the patients qualified for metabolic syndrome criteria.

hsCRP levels

The mean hsCRP levels in this study were 2.61±1.11mg/L. Sparse data is available regarding the normal levels of hsCRP levels in general population. Studies do indicate that a CRP level more than 1 mg/L is indicative moderate CAD risk. So a mean 2.61±1.11mg/L puts the study group as whole in risk for coronary artery disease. The levels of increased serum CRP correlates with the presence of traditional cardiovascular risk factors and may reflect contributions of these risk factors to vascular inflammation. So it is difficult to make a conclusion regarding

whether the fatty liver is an independent variable determining levels CRP in this study. A 2000 meta-analysis of 11 of the early population-based studies found a two-fold increase in relative risk (95% CI 1.6-2.5) for major coronary events between the upper and lower titers of hs-CRP, independent of clinical risk assessment or lipid profile. hsCRP being described as an independent risk factor for coronary artery disease, there could possibly be a common factor that is involved in CAD and fatty liver. Ndumele C etal [74] has found out hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation

According to AHA, low, intermediate, and high risk values were defined as <1, 1 to 3, and >3 mg/L. In this study 46 patients (68.7%) were found to have hsCRP values more than 1mg/L, while 14 (20.9%) had hsCRP values more than 3mg/L.

Only 7 among the study group had CRP values less than 1mg/L.

Another noticeable finding is the statistically significant high levels of hsCRP found in patients with metabolic syndrome. This is in line with other studies which show high levels of hsCRP in patients with metabolic syndrome. A Spanish study by Rodríguez-Leal etal found out that even though the hsCRP levels are high, use of hsCRP for the identification of hepatic inflammatory response in patients with Metabolic syndrome with NAFLD is limited because of its low sensibility and specificity observed on identifying different degrees of hepatic inflammation. [72]There is a moderate to strong positive correlation (r = 0.61) between the serum

levels of hsCRP and waist circumference. BMI and body weight also showed positive correlation, but not as strong as waist circumference. Waist circumference seems to be the best anthropometric measurement suited for our population for obesity risk classification. Another advantage is that it is easy to measure and the only equipment needed is measuring tape. Contrary to this, measuring BMI needs a weighing machine and height scale. And the calculation of the data (weight/height 2) also needs to be done.

The findings in this study are in line with others studies done on hsCRP and fatty liver. CRP levels and similar findings were noted in the ARIC study, which assessed the association of 19 novel risk markers including serum CRP with incident CHD in nearly 16, 000 adults followed for up to 15 years . Recently, a study reported increased serum levels of hs-CRP in cases of histologically confirmed NASH compared with simple non-progressive steatosis. A study by Zhou etal from China WD finds close correlation with hsCRP and insulin resistance. A study in Chilean hipsanic population finds higher hsCRP levels in patients with steatohepatitis. [73,74] James P. Luyendyk, Grace L. Guo s in his editorial on comments that the association between fatty liver disease and hs-CRP levels strongly suggests that assessing, preventing, and treating nonalcoholic fatty liver disease development is one potential strategy to reduce systemic inflammation and the risk of adverse cardiovascular outcomes in patients with metabolic syndrome. [75] Our results indicate that with further studies hs-CRP may

be considered as another non-invasive marker of NAFLD, adding a new tool to the repertoire of the primary care physicians and hepatologists attempting to establish a diagnosis of NAFLD.

7.Limitations of the study

1. The study population is derived from people who are attending health screening. They cannot be considered as representative of general population.
2. Due to limitations in logistics and technical capability, certain investigations like insulin levels, tranferrin saturation, serum iron levels, ferritin levels, and ceruloplasmin levels were not measured. Radiological fatty liver was not confirmed by liver biopsy, due to both technical limitations and relectance from the patients part to undergo an invasive procedure
3. The number of alcohol related fatty liver cases were very less, so not much statistically relevant data could not be obtained from that group.

8.Conclusions

1. Asymptomatic population diagnosed with fatty liver has a significant proportion of clinical and metabolic abnormalities.
2. All good number of patients had Obesity, Hypertension Diabetes, Prediabetes, and Dyslipidemias – all of these previously undetected abnormalities were newly diagnosed
3. Even though generalised malaise, right hypochondrial pain, hepatomegaly are considered to be prominent symptoms and signs of NAFLD, a good portion of fatty liver disease patients may be still living in the society without being detected, but harboring potential cardiovascular risk factors.
4. Asymptomatic patients need detailed evaluation and interventions since they have high prevalence of atherogenic and cardiovascular risk factors.
5. Alcoholics formed only a minor portion (8.9%) of the fatty liver group. That makes the rest 61 (91.1%) cases of Non Alcoholic Fatty Liver Disease.

6. Waist circumference seems to be the best parameter to quantify obesity and metabolic risk.
7. The AST and ALT levels, which are often used to diagnose and categories NALF and NASH were found to be having no significant associations with other variables in this study. This reimburses the fact that AST and ALT levels can vary even during course of the disease and it is not a sensitive or specific modality to diagnose NAFLD. It has to be supplemented by imaging or biopsy.
8. Not all NAFLD patients qualified for metabolic syndrome as per NCEP-ATP III criteria. Among them 19 patients qualified were diagnosed with metabolic syndrome.
9. Using the AHA classification CRP for coronary artery risk, 93% of the study populations are at risk of development of atherosclerotic, coronary artery disease.
10. CRP has a moderate to strong positive correlation to the waist circumference, BMI and weight in the study group ie CRP values tend to increase with obesity.
11. CRP levels are significantly high in patients with Fatty liver disease associated with metabolic syndrome.
12. CRP may be useful in risk stratification of Fatty liver disease. A long term prospective study will be needed to validate this.

13. Further research into CRP and other pro-inflammatory markers in fatty liver disease may provide vital information regarding the pathogenesis of fatty liver disease and has the potential of opening up new avenues for targeted treatment.

9. Bibliography

1. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver diseases: is biopsy necessary? Eur J Gastroenterol Hepatol 2003;15;539-43.
2. Tarantino G. Is NAFLD an incidentaloma? Gastroenterology 2006;130:1014-
3. Mark Feldman MD , Bruce F. Scharschmidt MD , Marvin H. Sleisenger MD, Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology,Diagnosis,Management.
4. Flack-Ytter Y, Younossi ZM, Marchesini G, MC Cullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver DIs 2001;21:17-26
5. Brunt EM, Tiniakos DG. Alcoholic and nonalcoholic fatty liver disease. IN: Odze RD, Goldblum JR, eds. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas 2nd ed. Philadelphia : Elsevier;2009:1007-14

6. Farrell GC. Non alcoholic steatohepatitis: What is it, and why is it important in the Asia Pacific Region? J Gastroenterol Hepatol 2003:18;124-38
7. Ludwig J, Viggiano T, McGill D, Ott B: Nonalcoholic steatohepatitis. Mayo clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55:434-8
8. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterology*. Sep 2009;137(3):865-72
9. Bacon BR, Farahvash MJ, Janney CG, Neuschwander Teteri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gasteroenterology 1994;107:1103-9
10. Amarapurkar D, Kamani P, Patel N, et al: Prevalence of non-alcoholic fatty liver disease: Population based study. Ann Hepatol 2007; 6:161-3
11. Park S, Jeon W, Kim S, et al: Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol 2006; 21:138-43.
12. Flores Y, Yee HJ, Leng M, et al: Risk factors for chronic liver disease in blacks, Mexican Americans, and whites in the United States: Results from NHANES IV, 1999-2004. Am J Gastroenterol 2008; 103:2231-8.

13. Matteooni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCollough AJ. Nonalcoholic fatty liver diseases: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413-9

14. Duseja A, Das A, Das R, et al. Clinicopathological proile of Indian patients with nonalcoholic fatty liver disease is different from the west. Dig Dis Sci 2007;52:2368-74.

15. Farrell GC, Larter CZ: Nonalcoholic fatty liver disease: From steatosis to cirrhosis. Hepatology 2006; 43:S99-S112.

16. Hsiao PJ, Kuo KK, Shin SJ, et al: Significant correlations between severe fatty liver and risk factors for metabolic syndrome. J Gastroenterol Hepatol 2007; 22:2118-23.

17. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007;11:1-16

18. Duseja A, Das A, Dhiman RK, et al. Indian patients with NAFLD presenting with raised transaminases are different at presentation. World J Gastroenterol 2007;13:649-50.

19. Pathology of fatty liver disease. AU - Brunt EM , Mod Pathol. 2007 Feb;20 Suppl 1:S40-8

20. Nonalcoholic steatohepatitis: definition and pathology. Brunt EM, Semin Liver Dis. 2001;21(1):3

21. Lefkowitch JH, Haythe J, Regent N. Kupffer cell aggregation and perivenular distribution in steatohepatitis. Mod Pathol 2002;15:699-704

22. Feldstein AE, Werneburg NW, Canbay A, et al: Free fatty acids promote hepatic lipotoxicity by stimulating TNF expression via a lysosomal pathway. Hepatology 2004; 40:185-94.

23. Gramlich T, Kleiner D, McCullough A, et al: Pathologic features associated with fibrosis in nonalcoholic fatty liver disease. Hum Pathol 2004; 35:196-

24. Flack-Ytter Y, Younossi ZM, Marchesini G, MC Cullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver DIs 2001;21:17-26

25. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007;11:1-16

26. Adams LA, Lymp JF, St. Sauver J, et al. The natural history of non-alcoholic fatty liver diseases - a population-based cohort study. Gastroenterology 2005;129:113-21

27. Ekstedt M, Franzen LE, Mathiensen UI, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-

28. Caldwell SH, Oliveira PMS, de Lima VMR, Park SH. NASH, cryptogenic cirrhosis and hepatocellular carcinoma, In: Bataller R, ed. International Update on Hepatology, Permanyer Publication; 2007.

29. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation 2002; 106:3143

30. Ogden C, Yanovski S, Carroll M, Flegal K: The epidemiologyof obesity. Gastroenterology 2007; 132:2087-102.

31. Carter-Kent C, Zein NN, Feldstein AE: Cytokines in the pathogenesis of fatty liver and disease progression to steatohepatitis: Implications for treatment. Am J Gastroenterol 2008; 103:1036-42.

32. Zafrani E: Non-alcoholic fatty liver disease: An emerging pathological spectrum. Virchows Arch 2004; 444:3-12.

33. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a hisological scocring system for nonalcoholic fatty liver disease Hepatology 2005;41:1313-12

34. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a hisological scocring system for nonalcoholic fatty liver disease Hepatology 2005;41:1313-12

35. Gramlich T, Kleiner D, McCullough A, et al: Pathologic features associated with fibrosis in nonalcoholic fatty liver disease. Hum Pathol 2004; 35:196

36. Ramanchandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Metabolic syndrome in urban Asian Indian adults – a population study using modified ATP-II criteria. Diabetes Res Clin Pract 2003;60:199-204.

37. Deepa R, Shanthirani CS, Premalatha G, Sastry NG, Moahan V. Prevalence of insulin resistance syndrome in a selected south Indian population- the Chennai urban population study – 7 [CUPS-7]. Indian J Med Res 2002;115:118-27.

38. Ratziu V, Giral P, Charlotte F, et al: Liver fibrosis in overweight patients. Gastroenterology 2000; 118:1117-23.

39. Mark Feldman MD , Bruce F. Scharschmidt MD , Marvin H. Sleisenger MD ,Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology,Diagnosis,Management.

40. Stranges S, Dorn J, Muti P, et al: Body fat distribution, relative weight, and liver enzyme levels: A population-based study. Hepatology 2004; 39:754-63

41. David Sutton , Textbook of Radiology and Imaging, 7ed International 2003

42. Ronald G. Grainger MB ChB(Hons) MD FRCP DMRD FRCR FACR(Hon) FRACR(Hon) (Editor), David J. Allison BSc MD MRCS LRCP MB BS DMRD FRCR FRCP (Editor), Adrian K. Dixon MD FRCR FRCP FRCS FMedSci FFRRCSI(Hon) FRANZCR(Hon) (Editor)Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging

43. Noninvasive assessment of hepatic fibrosis . Michael P Curry, MD ,Nezam H Afdhal, MD, FRCPI, Section Editor Bruce A Runyon, MD , Deputy Editor - Peter A L Bonis, MD. Uptodate clinical reference 19.1

44. Neuschwander-Tetri B, Caldwell S: Nonalcoholic steatohepatitis: Summary of an AASLD single topic conference. Hepatology 2003; 37:1202-19.

45. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Imbert-Bismut F; Ratziu V; Pieroni L; Charlotte F; Benhamou Y; Poynard T
Lancet 2001 Apr 7;357(9262):1069-75.

46. Stranges S, Dorn J, Muti P, et al: Body fat distribution, relative weight, and liver enzyme levels: A population-based study. Hepatology 2004; 39:754-

47. Mofrad P, Contos MJ, Haque M, et al: Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003; 37:1286-92

48. Siegelman E, Rosen MA: Imaging of hepatic steatosis. Semin Liver Dis 2001; 21:71-80

49. Saadeh S, Younossi Z, Remer E, et al: The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123:745-50.

50. Mishra A, Mishra R. Asian Indians and insulin resistance syndrome: Global perspective. Med Syndr and Rel Disord 2003;1:277-8

51. Andersen T, Gludd C, Franzmann ME, et al. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol 1991-;12:224-9

52. Houmard JA, Tanner CJ, Slentz CA, et al. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004;96;101-6

53. Angelico F, Burattin M, Alessandri C, et al. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. Chochrane Databse Syst Rev 2007:CD005166.

54. Microvesicular steatosis of the liver.

Hautekeete ML; Degott C; Benhamou JP ,Acta Clin Belg 1990;45(5):311-26

55. Clinical syndromes of alcoholic liver disease.

Adachi M; Brenner DA Dig Dis. 2005;23(3-4):255-63.

56. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2.

Roberts WL; Moulton L; Law TC; Farrow G; Cooper-Anderson M; Savory J; Rifai N Clin Chem 2001 Mar;47(3):418-25.1

57. Kushner, I. The phenomenon of the acute phase response. Ann N Y Acad Sci 1982; 389:39.1

58. Pearson, TA, Mensah, GA, Alexander, RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107:499.

59. Pearson, TA, Mensah, GA, Alexander, RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice:

A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107:499

60. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Ridker PM Circulation 2001 Apr 3;103(13):1813-8.

61. Amarapukar DN, Amaapurkar A. Non alcoholic statohepatitis clinicopathological profile. JAPI 2000;48;311-3

62. Bhat G, Pnadey, Baba CS et al. Metabolic syndrome in NAFLD patients an Indian perspective.

63. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey Ramachandran, C. Snehalatha, A. Kapur, V. Vijay, V. Mohan, A. K. Das, P. V. Rao, C. S. Yajnik, K. M. Prasanna Kumar and Jyotsna D. Nair, et al.

64. Non-alcoholic fatty liver disease in the Asia-Pacific region: Definitions and overview of proposed guidelines.Chitturi S; Farrell GC; Hashimoto E; Saibara T; Lau GK; Sollano JDJ Gastroenterol Hepatol. 2007 Jun;22(6):778

65. The natural history of nonalcoholic Fatty liver disease: a population-based cohort study. Adams LA; Lymp JF; St Sauver J; Sanderson SO; Lindor KD; Feldstein A; Angulo P Gastroenterology 2005 Jul;129(1):113-21

66. Fan JG, Zhu G, Li XJ, et al. Prevalence of and risk factors for fatty liver in a general population of Shanghai China. J Hepatol 2—5;43:508-13.

67. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT valuesPouneh Mofrad, Melissa J. Contos,Mahmadul Haque, Carol Sargeant,Robert A. isher, Velimir A. Luketic[1],Richard K. Sterling, Mitchell L. Shiffman,Richard T. Stravitz, Professor of Medicine Arun J. Sanyal M.D.

68. The relationship between serum transaminase activities and fatty liver in children with simple obesity.Noguchi H, Tazawa Y, Nishinomiya F.

69. Mildly Elevated Liver Transaminase Levels in the Asymptomatic Patient Paul t Gibony., Keck School of Medicine, University of Southern California, Los Angeles, California

70. Ramachandran A *et al.* Clustering of cardiovascular risk factors in urban Asian Indians. *Diabet Care* 1998; 21: 967–971.

71. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: The Framingham heart studyElizabeth K. Speliotes Joseph M. Massaro Udo HoffmannRamachandran S. VasanJames B. Meig Dushyant V. SahaniJoel N. HirschhornChristopher J. O'Donnell[3]Caroline S. Fox

72. Assessment of high sensitivity C-reactive protein (HS-CRP) as a marker of liver inflammation in patients with metabolic syndrome.- Rodríguez-Leal

GA, Morán S, Gallardo I, Milke P, Guevara-González L.Source - Clínica de Gastroenterología, Hospital Medica Sur, México, DF.

73. Non-alcoholic fatty liver, high sensitivity C reactive protein and insulin resistance. Zhou WD, Yang YL, Che ZH.Department of Endocrinology of Second Xiangya Hospital, Institute of Metabolism and Endocrinology, Diabetes Center, Metabolic Syndrome Research Center, Central South University, Changsha 410011, China

74. Ndumele CE, Nasir K, Conceicao RD, Carvalho JA, Blumenthal RS, Santos RD Hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation. Arterioscler Thromb Vasc Biol. 2011;31:1927–1932.

75. EditorialsSteatosis DeLIVERs High-Sensitivity C-Reactive Protein - James P. Luyendyk, Grace L. Guo Atherosis, thrombosis and vascular biology.

ABBREVIATIONS

ALP - Alkaline phosphatase

ALT - Alanine Aminotransferase

AST - Aspartate Aminotransferase

CRP - C Reactive Protein

HDL - High density lipoprotein

hsCRP - High sensitivity C reactive protein

LDL - Low density lipoprotein

MS - Metabolic Syndrome

T.B - Total Bilurubin

TC - Total Cholestrol

TG – Triglycerides

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A study on serum levels of C- Reactive protein and its Relation to clinical and laboratory profile of Asymptomatic cases diagnosed with fatty liver disease By Radiological screening

Principal Investigator : Dr.Deepu Sebin

Designation : PG in MD(GM)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 19.11.2010 at the Modernized Seminar Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate form the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

22/12/11

Profoma

Sl. No-
Date –
OP No–
Unit –

Name –

Age -
Sex -
Address-

Contact No-

Occupation-

Annual Income-

Diet- Vegetarian
Non vegetarian

Past History

DM Yes/No
SHT Yes/No
CAD Yes/No
CVA Yes/No
Jaundice
Yes/No
Any other
Significant Illness –

Drug Intake
Yes/No
If Yes, Name of drug| duration of drug

Personal History

Smoking Yes/No
Alcoholism Yes/No
if yes amount and duration

Confirmation by family member -

Clinical Examination

Pulse Rate:
BP :

Height -
Weight-
Waist Circumference-

Systems Examination

Hepatomegaly: Yes/No

_____cm

Spleen
Yes/No
_____cm

Investigations

FBS -
PPBS -

Fasting Lipid Profile
TC -
HDL -
LDL -
TG -

LFT
TB -
DB -
AST -
ALT -
ALP -

Total Protein-
S.Albumin-
S.Globuln -

Urine Albumin-

HbSAg-
positive/negative

Anti HCV-
positive/negative

hsCRP -

Master Chart – Page 1

N	OP No	Ag	S	A	WC	Wt	Ht	BMI	C	L	BPS	BPD	FBS	TC	TG	HD	LDL	TB	AS	AL	AP	B	C	CRP
1	4259	55	1	0	89	78	1.66	28.3	0	3	130	96	82	236	139	52	156	0.8	23	17	146	0	0	3.62
2	4559	36	1	0	96	77	1.67	27.6	0	0	120	70	90	210	112	60	128	0.7	26	30	40	0	0	4.5
3	4322	50	1	0	73	60	1.52	25.9	0	0	120	80	283	183	60	58	113	1	30	29	230	0	0	2.56
4	3211	43	0	0	74	70	1.73	23.3	0	0	128	70	90	176	70	56	106	0.8	25	18	76	0	0	1.81
5	4915	52	0	0	86	72	1.62	27.4	0	0	130	90	74	196	143	32	135	0.6	34	22	82	0	0	1.08
6	23440	35	0	1	88	76	1.71	25.9	0	4	126	80	99	222	78	50	156	2	110	186	160	0	0	1.08
7	4515	30	1	0	79	57	1.6	22.2	0	0	118	76	92	212	126	36	151	0.8	45	38	77	0	0	1.08
8	4639	39	1	0	104	82	1.59	32.4	0	0	160	110	112	330	212	43	245	1	56	67	90	0	0	4.08
9	4526	42	1	0	82	65	1.53	27.7	0	0	140	90	78	246	130	40	180	0.8	34	23	101	0	0	1.73
10	23126	44	0	0	70	60	1.59	23.7	0	0	120	80	89	202	139	59	115	0.8	23	22	38	0	0	2.45
11	3400	55	0	0	76	65	1.59	25.7	0	0	128	80	78	283	174	30	218	0.8	33	31	90	0	0	1.06
12	4026	46	0	0	80	70	1.7	24.2	0	0	120	80	70	212	102	50	138	1	22	12	68	0	0	2.86
13	23455	32	1	0	72	68	1.63	25.5	0	0	100	70	55	310	286	44	209	0.8	44	52	75	0	0	1.51
14	994	70	0	1	68	48	1.65	17.6	0	0	100	70	186	210	127	45	140	0.8	35	44	112	0	0	2.1
15	2119	65	1	0	72	60	1.55	24.9	0	0	130	80	76	246	155	77	138	1.8	43	55	134	0	0	1.08
16	4470	76	0	0	78	70	1.75	22.8	0	0	180	120	76	150	76	54	81	0.7	33	29	108	0	0	3.22
17	4444	56	1	0	96	80	1.59	31.6	0	0	140	90	140	190	110	47	121	1	45	54	356	0	0	2.45
18	2401	72	1	0	68	58	1.62	22.1	0	0	122	80	98	210	100	48	142	0.7	18	16	79	0	0	1.28
19	4217	78	0	0	80	55	1.57	22.3	0	0	130	90	112	183	112	50	111	0.6	24	19	89	0	0	2.24
20	4510	45	1	0	82	66	1.46	30.9	0	0	140	90	110	165	102	50	95	1	40	22	126	0	0	1.1
21	3367	59	1	0	75	48	1.69	16.8	0	0	110	70	79	156	78	55	85	0.7	22	24	112	0	0	1.82
22	3245	49	1	0	84	61	1.72	20.6	0	0	176	108	94	228	148	41	157	1.2	18	23	87	0	0	2.12
23	234098	40	0	0	94	70	1.72	23.6	0	0	130	90	110	256	170	36	186	0.7	45	55	108	0	0	4.82
24	342	47	0	1	76	69	1.58	27.6	0	0	130	80	96	186	66	53	120	2	22	26	113	0	0	2.33
25	4683	72	1	0	75	52	1.53	22.2	0	0	140	90	78	189	110	50	117	0.7	18	22	107	0	0	2.3
26	4196	41	1	0	89	79	1.62	30.1	0	0	150	95	106	242	160	32	178	0.7	28	31	61	0	0	2.06
27	223601	64	1	0	98	70	1.5	31.1	0	0	136	90	116	202	136	45	130	0.8	56	47	118	0	0	3.08
28	2383	49	1	0	84	73	1.57	29.6	0	0	130	90	98	156	83	67	72	7	33	38	82	0	0	2.12
29	3456	39	1	0	104	67	1.44	32.3	0	3	126	80	85	212	136	49	136	0.6	36	34	107	0	0	2.12
30	2467	43	0	1	77	79	1.68	27.9	0	2	124	84	83	190	68	65	111	0.8	36	40	74	0	0	1.45
31	2349	67	1	0	66	67	1.7	23.1	0	0	140	90	140	210	110	43	145	1.4	32	28	134	0	0	1.05
32	12472	42	1	0	78	59	1.59	23.3	0	0	150	100	70	153	70	50	89	0.8	23	22	98	0	0	1.1
33	4119	60	1	0	89	76	1.64	28.2	0	0	110	70	88	210	130	32	152	0.8	21	22	60	0	0	1.71
34	660	62	0	0	112	106	1.61	40.8	0	0	140	90	92	260	208	42	176	0.8	32	28	58	0	0	2.85
35	4433	39	0	0	108	94	1.71	32.1	0	0	126	80	90	225	186	34	154	0.8	35	28	136	0	0	4.08
36	4474	32	0	0	90	74	1.58	29.6	0	2	110	80	91	226	140	35	163	0.7	23	30	212	0	0	1.02
37	4911	48	1	0	76	59	1.58	23.6	0	0	150	100	98	270	310	44	164	0.9	77	43	106	0	0	1.08
38	4612	38	1	0	84	72	1.6	28.1	0	0	119	70	110	328	56	70	247	0.7	34	56	93	0	0	2.12
39	5033	29	1	0	94	82	1.75	26.7	0	0	130	90	94	240	163	40	167	0.6	23	25	192	0	0	2.04

Master Chart – Page 2

N	OP No.	Ag	S	A	WC	Wt	Ht	BMI	C	L	BPS	BPD	FBS	TC	TG	HD	LDL	TB	AS	AL	AP	B	C	CRP
40	4135	45	0	0	84	70	1.5	31.1	0	0	120	80	86	160	76	51	94	1.2	21	18	83	0	0	2.85
41	4549	58	0	0	74	58	1.63	21.8	0	0	110	70	130	180	110	58	100	1	28	34	40	0	0	0.48
42	5042	40	1	1	112	98	1.6	38.2	0	3	130	90	79	280	189	33	209	1	22	26	108	0	0	3.72
43	8832	55	0	1	94	64	1.7	22.1	0	0	110	70	89	182	100	56	106	1.9	43	23	108	0	0	1.06
44	3444	66	1	0	72	68	1.69	23.8	0	0	126	80	56	170	86	58	95	0.8	21	20	50	0	0	2.42
45	2135	39	1	0	76	64	1.62	24.3	0	0	110	70	89	160	86	59	86	1	12	22	194	0	0	1.22
46	23319	37	0	0	112	98	1.76	31.6	0	0	136	90	86	326	173	46	245	1.4	50	52	128	0	0	3.89
47	4664	51	0	0	96	77	1.58	30.8	0	0	150	110	225	216	180	48	132	0.8	53	32	88	0	0	2.83
48	4090	31	1	0	84	80	1.7	27.6	0	0	120	89	90	210	132	48	136	0.8	18	16	178	0	0	0.86
49	4357	34	1	0	80	71	1.66	25.7	0	0	126	76	84	220	140	54	138	0.8	45	46	184	0	0	1.18
50	113445	43	1	0	76	48	1.47	22.2	0	0	110	70	88	172	69	40	118	0.7	18	22	89	0	0	0.86
51	4168	22	0	0	92	68	1.53	29.0	0	0	112	70	89	210	132	45	139	0.8	26	22	63	0	0	2.4
52	3402	58	1	0	96	76	1.53	32.4	0	0	140	90	96	226	163	60	133	1	42	40	85	0	0	3.21
53	601	42	1	0	70	44	1.43	21.5	0	0	110	70	81	160	141	50	82	1	24	33	122	0	0	1.83
54	54567	51	1	0	80	69	1.68	24.4	0	0	126	80	90	181	110	56	103	0.8	50	44	80	0	0	2.96
55	2001	44	0	0	86	74	1.75	24.1	0	0	130	90	94	240	140	36	176	0.7	25	21	110	0	0	1.12
56	31076	56	1	0	98	84	1.64	31.2	0	0	140	90	88	308	224	34	229	0.8	25	22	44	0	0	3.86
57	4777	63	1	0	76	47	1.46	22.0	0	0	150	110	225	194	80	47	131	1	32	27	90	0	0	2.08
58	4132	35	1	0	112	102	1.58	40.8	0	0	130	90	90	248	160	36	180	0.6	24	22	100	0	0	4.59
59	3210	55	0	0	80	77	1.61	29.7	0	0	126	86	72	177	88	55	104	1	19	22	72	0	0	0.68
60	262335	43	0	0	82	68	1.68	24.0	0	0	160	110	129	187	105	49	117	0.4	33	38	67	0	0	2.98
61	4848	40	1	0	68	48	1.42	23.8	0	0	120	80	89	158	70	58	86	0.7	23	20	126	0	0	1.88
62	4198	39	1	0	76	69	1.65	25.3	0	0	136	82	101	170	70	60	96	0.7	23	30	80	0	0	3.6
63	2112	50	0	0	80	62	1.56	25.4	0	0	130	90	87	180	110	43	115	0.7	18	20	213	0	0	0.65
64	4465	37	1	0	69	55	1.54	23.1	0	0	128	80	120	195	160	38	125	0.9	43	26	98	0	0	0.8
65	4656	48	1	0	108	78	1.5	34.6	0	0	156	100	106	250	170	56	160	0.9	35	36	182	0	0	3.91
66	4657	44	0	0	92	84	1.64	31.2	0	0	130	90	167	280	170	45	201	0.9	40	34	55	0	0	1.83
67	4630	49	1	0	70	48	1.65	17.6	0	0	110	70	98	172	62	61	99	0.6	22	18	101	0	0	0.86

Key to master chart

N – Serial Number

OP No.- Op number

Ag – Age

S – Sex (Male 0, Female 1)

A – Alcohol Intake (0 – No, 1 – yes)

WC – Waist Circumference

Ht – Height

Wt- Weight

BMI – Body Mass Index

C – Significant Clinical Features

L – Liver size (in cms)

BPS – Blood pressure , Systolic

BPD – Blood pressure, Diastolic

FBS – Fasting Blood Sugar

TC – Total Cholesterol

TG – Triglycerides

HD – High density lipoproteins

LDL – Low density lipoproteins

TB – Total bilurubin

AS – Aspartate aminotransferase

AL- Alanine aminotransferase

AP – Alkaline phosphatase

B – HbSAg

C – Anti HCV

CRP – High Sensitive C reactive protein